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The South Carolina Collaborative Undergraduate HBCU Student Summer Training Program

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**Background:** There is a critical need to increase the racial/ethnic diversity of prostate cancer researchers. The goal of the Training Program is to provide research training activities to **12** students over a 3-year period from three Historically Black Colleges and Universities (HBCUs) in South Carolina: Claflin University, South Carolina State University, and Voorhees College. The three *aims* of the Training Program are: Aim 1.) To provide training in the basics of research design and methods to 12 Student Fellows each year from the three HBCUs; Aim 2.) To immerse 4 Student Fellows per year in prostate cancer research; Aim 3.) To implement a unique dual-level research mentoring strategy for the students. **Results:** During the current reporting period, 4 Student Fellows were identified, recruited to participate in the program, and admitted to the DOD South Carolina Collaborative Undergraduate HBCU Student Summer Training Program. The Student Fellows were matched with Research Mentors at MUSC, with whom they conducted research in the summer of 2012. Each Student Fellow prepared a scientific paper, gave a scientific presentation at the end of the summer program, and completed a 9-week Princeton Review Graduate Record Examination Test Preparation Course. In the summer of 2012, students at SCSU participated in summer program lectures via videoconference. **Conclusions:** State-of-the art comprehensive prostate cancer research education and training opportunities were provided to **4** Student Fellows from HBCUs in South Carolina. Each Student Fellow prepared a scientific paper and gave at least 1 scientific presentation. Nine Student Fellows gave scientific presentations, two of which were presented at national scientific meetings. A cadre of scientists who are well-prepared to conduct research spanning the continuum from basic science to clinical science to population-based research was developed.

**15. SUBJECT TERMS**

Prostate Cancer Research Training Program

Summer Undergraduate Research Program (SURP)

Student Fellows from Historically Black Colleges and Universities (HBCUs)

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## Table of Contents

	<u>Page</u>
<b>Introduction.....</b>	<b>6</b>
<b>Body.....</b>	<b>7</b>
<b>Key Research Accomplishments.....</b>	<b>8</b>
<b>Reportable Outcomes.....</b>	<b>12</b>
<b>Conclusions.....</b>	<b>18</b>
<b>References.....</b>	<b>N/A</b>
<b>Appendices A-C.....</b>	<b>21</b>
<b>Appendix A: Ernest E. Just Symposium Agenda.....</b>	<b>22</b>
<b>Appendix B: Ernest E Just Symposium Student Attendees.....</b>	<b>24</b>
<b>Appendix C: Summaries of Students' Abstracts.....</b>	<b>25</b>
<b>Appendix D: Academic Accomplishments to Date.....</b>	<b>157</b>





## INTRODUCTION

### **The Scientific Context of the Training Program**

The South Carolina Collaborative Undergraduate HBCU Student Summer Training Program (referred to as the Training Program) will provide a biomedical research training experience to 12 students over a three-year period (2012-2015) from three Historically Black Colleges and Universities (HBCUs) – Claflin University (CU), South Carolina State University (SCSU), and Voorhees College (VC). Undergraduate students from the three HBCUs (defined as Student Fellows) will participate in research intensive summer internships in the laboratories/research units of senior prostate cancer research scientists at the Medical University of South Carolina Hollings Cancer Center (MUSC HCC). This new Training Program application builds upon the success of the currently funded Department of Defense (DOD) prostate cancer research training program (2009-2011) and the long standing NIH funded Summer Undergraduate Research Training Program at MUSC (1992-present). The inter-institutional leadership of these summer training efforts have carefully examined the formative and summative evaluations provided by previous Student Fellows, Mentors, and Advisors in order to maximize the ability of this new enhanced program proposal to reach its ultimate goal – to increase the racial and ethnic diversity of emerging scientists who may choose prostate cancer research careers in basic, clinical, and population sciences. In this new application, the Training Program has been improved with a built-in, dual-level research and career mentoring strategy involving current graduate students and post-doctoral trainees included on the mentoring team; the addition of a clinical shadowing experience in the MUSC/HCC multidisciplinary genitourinary clinics and tumor board; more year-round opportunities for which the Student Fellows will participate; and an opportunity for Training Program alumni to continue relationships with new trainees going forward. Measurable outcomes of the Training Program will include the number of Student Fellows who take the Graduate Record Examination (GRE), apply to graduate school, and give scientific presentations and publish their research results in peer-reviewed scientific journals based on their summer research experience. Efforts will be made to capture long term outcomes as well as to determine how many Student Fellows choose to pursue a medical or biomedical focused graduate and post graduate career.

The three Specific Aims are to:

- Aim 1. To provide training in the basics of research design and methods to 12 Student Fellows each year from the three HBCUs;
- Aim 2. To immerse 4 Student Fellows per year in prostate cancer research;
- Aim 3. To implement a unique dual-level research mentoring strategy for the students.

### **Program Director and Training Team**

Dr. Marvella E. Ford is the Program Director. Drs. Rebecca Bullard-Dillard (CU), Judith Salley (SCSU), and Leroy Davis (VC) are Associate Directors. This four-person leadership team collaborates closely in the management and administration of the award, as well as the continued development and enhancement of the Training Program. The Program Director and Associate Directors share scientific interests in health disparities, serve in other leadership roles within their institutions, and meet frequently, both formally and informally. These individuals form the Executive Committee for the Training Program. Each institution has appointed Faculty Advisors consisting of Dr. Leslie Wooten-Blanks (CU), Dr. James B. Stukes (SCSU), and Mrs. Gayle Tyler Stukes (VC).

## **BODY**

### **Statement of Work**

#### **Task 1. Identify and Recruit the Student Fellows**

- (a) Identify the pool of potential Student Fellows (Year 1, months 1-3)
- (b) Interview the potential Student Fellows (Year 1, months 1-3)
- (c) Select the top Student Fellows (Year 1, months 1-3)
- (d) Match the Student Fellows with their Research Mentors at MUSC (Year 1, months 1-3)
- (e) Hold the Kickoff Intensive and Luncheon (Year 1, months 4-6)

**Deliverables:** Four Student Fellows per year were identified, recruited to participate in the program, and matched with senior prostate cancer research mentors at MUSC.

#### **Task 2. Provide Training in Biomedical and Prostate Cancer Research**

- (a) Conduct Aim 1: Training in the Basics of Research Design and Methods through participation in the MUSC Summer Undergraduate Research Program (Year 1, months 6-8)
- (b) Conduct Aim 2: Prostate Cancer Research Training (Year 1, months 6-8)
- (c) Sponsor the Student Fellows' Participation in a Graduate Record Examination (GRE) course (Year 1, months 6-8)

**Deliverables:** We provided state-of-the art comprehensive prostate cancer research education and training opportunities for 4 students from three of South Carolina's HBCUs. We have developed a cadre of scientists who are well-prepared to play a significant role in discovering and testing new prostate cancer biomarkers. These investigators will conduct research spanning the continuum from basic science to clinical science to population-based research. At least 75% of the Student Fellows will take the GRE and at least 75% of the Student Fellows will apply to graduate school.

#### **Task 3. Prepare Tangible Scientific Products**

- (a) Prepare and present scientific abstracts based on the Student Fellows' prostate cancer research (Year 1, months 10-12)
- (b) Prepare manuscripts that will be submitted to peer-reviewed journals (Year 1, months 10-12)

**Deliverables:** At least 4 scientific presentations will be conducted by Student Fellows. At least 2 peer reviewed publications will result.

#### **Task 4. Evaluate the Training Program**

- (a) Assess the number of applicants to the Training Program (Year 1, months 1-4)
- (b) Assess the number of Student Fellows who apply to graduate school (Year 1, months 1-12)
- (c) Assess the number of Student Fellows who are admitted to graduate school (Year 1, months 1-12)
- (d) Assess the number of graduate schools to which Student Fellows are admitted (Year 1, months 1-12)
- (e) Employ several tracking mechanisms to monitor the scientific progress of the students, including:
  - 1. Searching the MUSC graduate program databases to identify whether any of the students applied, were offered, or accepted positions at MUSC.
  - 2. Contacting the participating universities' alumni offices.
  - 3. Employing other internet based search tools/communications (Google, MySpace, Facebook, and Historically Black College/University Connections, etc.) to identify students' current locations, contact information, and academic achievements (Year 1, months 10-12)
- (f) Identify the number of scientific abstracts presented and peer-reviewed publications that result (Year 1, months 10-12)

**Deliverables:** We will prepare a document assessing the tangible products that result from the Training Program.

## KEY RESEARCH ACCOMPLISHMENTS

### **Task 1. Identify and Recruit the Student Fellows**

**(a) Identify the pool of potential Student Fellows (Year 1, months 1-3)**

**(b) Interview the potential Student Fellows (Year 1, months 1-3)**

**(c) Select the top Student Fellows (Year 1, months 1-3)**

To accomplish Tasks 1(a) – 1(c), Dr. Ford, the Program Director worked with Associate Directors Drs. Rebecca Bullard-Dillard (Claflin University), Dr. Judith Salley (SC State University), and Dr. Leroy Davis (Voorhees College) as well as Faculty Advisors Dr. Leslie Wooten-Blanks (Claflin University), Dr. James Stukes (SC State University), and Mrs. Gayle Stukes (Voorhees College) to identify potential Student Fellows. The Associate Directors and Faculty Advisors issued a call for applicants to their student bodies and personally approached students whom they felt would be outstanding applicants for the summer research program. For example, Drs. Ford (Principal Investigator), Bullard-Dillard (Associate Director), Salley (Associate Director), and Davis (Associate Director) communicated via electronic mail to discuss the 2012 SURP application process and deadlines.

To cite another example, to broaden the pool of potential applicants, each Associate Director invited faculty and students from his/her institution to participate in the Ernest Just Symposium held on February 24, 2012 at MUSC. A total of 220 students participated, including 65 students from HBCUs in South Carolina (Table 1.). The 220 students represented 21 different high schools, colleges and universities. A total of 65 students from HBCUs in SC participated in the Symposium, as well as 75 students from HBCUs in other regions of the country. The agenda from the Symposium and the number of students from each institution are included in Appendices A-B. Dr. Salley was instrumental in recruiting HBCU students from across the U.S. The students who participated in the Symposium also received a tour of scientific research units at MUSC and met with MUSC faculty members who could become their future research mentors.

**(d) Match the Student Fellows with Their Research Mentors at MUSC (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)**

In Year 1, the Student Fellows were matched with their Research Mentors at MUSC based on the expressed interests of the Student Fellows as stated in their written MUSC Summer Undergraduate Research Program (SURP) applications. The following tables show the names of the students who participated in the DOD South Carolina Collaborative Undergraduate HBCU Student Summer Training Program, their Research Mentors at MUSC, and their research topics.

<b>Summer 2012 DOD South Carolina Collaborative Undergraduate HBCU Student Summer Training Program Students, Mentors, and Research Topics</b>			
<b>Student Name</b>	<b>Academic Institution</b>	<b>MUSC Research Mentor</b>	<b>Research Topic</b>
Ms. Myshayla Bell	Claflin University	Dr. Shikhar Mehrotra	Overexpression of an Antigen in Melanoma Tumors and the Surrounding T Regulatory Cells using Immunohistochemistry
Ms. Jasmine Fox	SC State University	Dr. Erika T. Brown	The Role of RAD51 in Triple Negative Breast Tumor Progression/Relationship Between Breast Cancer and Metabolic Syndrome
Ms. Claudia Thompson	SC State University	Dr. Danyelle Townsend	The Effects of PDI Inhibitors on S-Glutathionylation in Prostate Cancer Cells
Ms. Britney White	Claflin University	Dr. Patrick Woster	Cancer Epigenetics: Using MTS Assays to determine cytotoxicity in drugs containing LSD1 and DNA methylation inhibitors

In addition to the students listed above, the Director and Associate Directors leveraged funding from two other grants to support an additional three students:

<b>Summer 2012 DOD South Carolina Collaborative Undergraduate HBCU Student Summer Training Program Additional Students, Mentors, Funding Sources, and Research Topics</b>				
<b>Student Name</b>	<b>Academic Institution</b>	<b>MUSC Research Mentor</b>	<b>Funding Source</b>	<b>Research Topic</b>
Ms. Sylvia Bridges	SC State University	Dr. Victoria Findlay	DOD - Southeastern Virtual Institute for Health Equity and Wellness (PI: Slaughter; Project PI: Ford)	The Effects of MiRNA on Prostate Cancer
Ms. Laila Green	Claflin University	Dr. Marvella Ford	DOD - Southeastern Virtual Institute for Health Equity and Wellness (PI: Slaughter; Project PI: Ford)	Improving Perceptions of Cancer Clinical Trials in South Carolina
Ms. Deidra White	SC State University	Dr. Dave Turner	NIH/NCI P20 South Carolina Cancer Disparities Research Center (PIs: Ford and Salley)	Implications of DNA Glycation Affecting Correlation of Racial Disparities in Prostate Cancer

**(e) Hold the Kickoff Intensive and Luncheon (Year 1, months 4-6; Year 2, months 4-6; Year 3, months 4-6)**

The Kickoff Intensive and Luncheon took place during the first meeting of the didactic training program in prostate cancer research. Dr. Marvella E. Ford, Associate Director from the MUSC Hollings Cancer Center and Ms. Tonya Hazelton, who coordinates the DOD Training Program, gave an overview of the DOD South Carolina Collaborative Undergraduate HBCU Student Summer Training Program.

**Task 1 Deliverables:** Four Student Fellows (plus an additional three students who were supported using leveraged funds) were identified, recruited to participate in the program, and admitted to the DOD South Carolina Collaborative Undergraduate HBCU Student Summer Training Program. The Student Fellows were matched with Research Mentors at MUSC, with whom they conducted research in the summer of 2012.

**Task 2. Provide Training in Biomedical and Prostate Cancer Research**

**(a) Conduct Aim 1: Training in the Basics of Research Design and Methods through participation in the MUSC Summer Undergraduate Research Program (Year 2, months 6-8)**

The Student Fellows participated in an intensive training program in the Basics of Research Design and Methods through participation in the MUSC Summer Undergraduate Research Program (SURP). The following tables show the SURP curriculum from 2012

**Summer Undergraduate Research Program (SURP) Lecture Series**  
**Summer 2012**

<u><i>Date</i></u>	<u><i>Topic</i></u>	<u><i>Lecturer</i></u>
	<u>Responsible Conduct of Research – MANDATORY</u>	
June 1	What is Translational Research?	Kathleen T. Brady, M.D., Ph.D.
June 2	The Development of a New Treatment and Diagnostic Test for Bladder Cancer: From Bench to Bedside	Omar Moussa, PhD
June 3	Human Subject Research Success Center: How Scientists Get Help Conducting Research/ Examples of Translational Research	Susan C. Sonne, PharmD Royce Sampson, MSN, RN
	Research/Examples of Translational Research	
	<u>Responsible Conduct of Research – MANDATORY – 8:30 – 10:20 am</u>	
June 6	MANDATORY: Public Perceptions of Scientific Research ("And the Band Played On") Questionable Research Practices (discussion of video)	Ed Krug, PhD Titus Reaves, PhD
June 7	Mandatory: Moral Reasoning in Ethical Dilemmas (lecture/case study/discussion) Mentoring (lecture and discussion) Responsible Lab Citizenship	Ed Krug, PhD
June 8	MANDATORY: <i>Data Management/Data Manipulation</i> & Mentoring (lecture/discussion) Authorship and Plagiarism (lecture/case/study/discussion)	Ed Krug, PhD
June 9	Animal Use in Research (lecture & discussion) Research Misconduct/Whistleblower Protections (lecture/case study/discussion)	Alison Smith, PhD Ed Krug, PhD
	Closing Comments/Exit Evaluation	
June 10	Treatment of Cocaine Addiction: From Bench to Bedside	TBA
June 13	Hepatic Steatosis in a Growing World: The Impact on Transplantation	Kenneth Chavin, MD
<u>Outside Assignment: Complete the University of Montana On-Line RCR training (link below) by June 13th – you must score a minimum of 70% on all quizzes. Bring paper copies of quiz completion with you to the RCR Lectures starting on June 6th. (<a href="http://ori.dhhs.gov/education/products/montana_round1/research_ethics.html">http://ori.dhhs.gov/education/products/montana_round1/research_ethics.html</a>)</u>		
June 14	Lipidomics	Maurizio Del Poeta, MD
June 15	Stem Cells	Amanda LaRue, PhD
June 16	Cell Biology – Tissue Ultrastructure	Debra Hazen-Martin, PhD
June 17	Developmental Biology	Michael Kern, PhD

June 20	Proteomics Technology	Lauren Ball, PhD
June 21	(H) The Heart	Perry Halushka, PhD, MD
June 22	Confocal/Multiphoton Microscopy of Living Cells and Tissues	John Lemasters, MD, PhD
June 23	(C) Cancer Cell Cycle	Cynthia Wright, PhD
June 24	Microarray Analysis	Jeremy Barth, PhD
June 27	Recombinant DNA	David Kurtz, PhD
June 28	Transcription	Steven Kubalak, PhD
June 29	(H) Electrical Properties of the Heart	Rupak Mukherjee, PhD
June 30	(C) Cytogenetics	Dayna Wolff, PhD
July 1	(N) Retinoids & Vision	Masahiro Kono, PhD-
July 5	G Proteins	John Hildebrandt, PhD
July 6	(H) Arterial Pressure Control & High Blood Pressure	Perry Halushka, PhD, MD
July 7	(N) Dementia	Mark Kindy, PhD
July 8	(N) ADD/ADHD	Antonieta Lavin, PhD
July 11	(C) Kinds of Cancer	Robert Gemmill, PhD
July 12	Receptors	Steven Rosenzweig, PhD
July 13	(N) Spinal Cord Injury	Narendra Banik, PhD
July 14	(H) Aspirin & NSAIDS	Perry Halushka, PhD, MD-
July 15	(C) Herbals & Cancer	Michael Wargovich, PhD-
July 18	(C) Cancer Disparities	Marvella Ford, PhD
July 19	(N) Addiction & Drugs	Kimber Price, PhD
July 20	(C) Epidemiology of Cancer	Kristin Wallace, PhD-
July 21	(H) Atherosclerosis	Samar Hammad, PhD
July 22	(C) Cancer Chemotherapy	David Kurtz, PhD
July 25	(N) Neuroimaging Lab Demonstration	TBA
July 26	(H) Kidney	Ed Soltis, PhD
July 27	(H) Imaging the Heart	Joseph Schoepf, MD
July 28	(N) Addiction & Alcohol	Corigan Smothers, PhD
July 29	(N) Schizophrenia	Antonieta Lavin, PhD

Note: Lectures in Black are for all students.

Lectures in Blue are for Cardiovascular track students. (7 lectures)

Lectures in Red are for Cancer track students. (7 lectures)

Lectures in Green are for Neuroscience track students. (8 lectures) CTSA – (5 lectures)



## **Conduct Aim 2: Prostate Cancer Research Training (Year 1, months 6-8)**

The Student Fellows participated in an intensive training 10-week program in Prostate Cancer Research. Lectures focused on population science, statistical methods in prostate cancer research, prostate cancer clinical research, and basic science research. Other lectures described funding opportunities available to the students, career development opportunities, qualitative research methods, perspectives of prostate cancer among community members, and tips for preparing graduate school applications. In addition, as prostate cancer is a hormone-related cancer and some of the biological mechanisms that impact the etiology and treatment of prostate cancer are also relevant to breast cancer, the curriculum included information pertaining to breast cancer as well.

The schedule also provided time for students to rehearse their research presentations and gain input from their mentors and other scientists at the HCC. Disparities research was a cross-cutting theme in all of the lectures.

The structure of the curriculum also provides the students with a better understanding of the different population groups that were included in their research. Therefore, cultural enrichment activities were added to the curriculum, such as the Gullah tour of Charleston, in order to expose the students to the local and historic culture of the Charleston population. The Sea Island (Gullah) population is a subpopulation of African Americans indigenous to the coastal regions of the eastern seaboard. They are the most genetically homogeneous group of blacks in the U.S. Their particularly low rate of European American genetic admixture makes this a unique population for basic, clinical and population-based research. The following tables show the Summer 2012 cancer research training curriculum.

**(c) Sponsor the Student Fellows' Participation in a Graduate Record Examination (GRE) course  
(Year 1, months 6-8)**

In 2012, all four Student Fellows took the 10-week Princeton Review GRE Test Preparation Course. The Princeton Review is a standardized test preparation company. The course met on Wednesday evenings from 5:30 pm – 8:30 p.m. The course seamlessly adjusts classwork and homework to the skill level of each student. This is accomplished by focusing on the areas where each student needs the most improvement. The course provides instruction in test-taking skills, and provides opportunities for dynamic group discussions and collaborative drills.

**Task 2 Deliverables:** In 2012, state-of-the art comprehensive prostate cancer research education and training opportunities were provided for 4 students from two of South Carolina's HBCUs. Funds were leveraged from other federally funded training grants to provide the same level of education and training to an additional 3 students from HBCUs in South Carolina. We are developing a cadre of scientists who are were-prepared to play a significant role in discovering and testing new prostate cancer biomarkers. In the future, these investigators will likely conduct research spanning the continuum from basic science to clinical science to population-based research.

**Task 3. Prepare Tangible Scientific Products**

- (a) Prepare and present scientific abstracts based on the Student Fellows' prostate cancer research (Year 1, months 10-12)**
- (b) Prepare manuscripts that will be submitted to peer-reviewed journals (Year 1, months 10-12)**
- (c) Develop manuscripts to describe the scope and outcomes of the project (Year 1, months 9-12)**

In 2012, each Student Fellow prepared a scientific research paper that will form the basis of a peer-reviewed publication. The Student Fellows are completing manuscripts with their research mentors. Each Student Fellow gave a scientific presentation based on the results of his or her work.

Summaries of each Student Fellows' research projects are included in **Appendix C**. A manuscript describing the scope and outcomes of the Training Program will be initiated in the spring of 2012.

**Deliverables:** A total of 9 scientific presentations were made by the Student Fellows, including one presentation at national scientific meetings.

**Task 4. Evaluate the Training Program**

- (a) Assess the number of applicants to the Training Program (Year 1, months 1-4)**

In the spring of 2012, 16 students from South Carolina's HBCUs applied to the DOD South Carolina Collaborative Undergraduate HBCU Student Summer Training Program. As planned, four Student Fellows were selected who were funded through the DOD South Carolina Collaborative Undergraduate HBCU Student Summer Training Program enrolled in the Training Program in the summer of 2012. An additional three Student Fellows were selected. Their participation in the Training Program was supported through leveraged funds from a DOD Southeastern Virtual Institute for Health Equity and Wellness grant and an NIH/NCI P20 South Carolina Cancer Disparities Research Center grant.

**(b) Assess the number of Student Fellows who apply to graduate school (Year 1, months 1-12)**

The Student Fellows who participated in the 2012 DOD South Carolina Collaborative Undergraduate HBCU Student Summer Training Program were rising sophomores through seniors. As described below, we are employing several strategies to monitor the Student Fellows' progression through their academic careers.

**(c) Assess the number of Student Fellows who are admitted to graduate school (Year 1, months 1-12) and (d) Assess the number of graduate schools to which Student Fellows are admitted (Year 1, months 1-12)**

We are actively keeping track of the progress of the Student Fellows using the strategies that are described below.

**(e) Employ several tracking mechanisms to monitor the scientific progress of the students, including:**

- 1. Searching the MUSC graduate program databases to identify whether any of the students applied, were offered, or accepted positions at MUSC.**
- 2. Contacting the participating universities' alumni offices.**
- 3. Employing other internet based search tools/communications (Google, MySpace, Facebook, and Historically Black College/University Connections, etc.) to identify students' current locations, contact information, and academic achievements (Years 2, 3, and beyond)**

We have implemented several steps for tracking student scientific progress. Communication and assistance from the Associate Directors and Faculty Advisors have proved to be very effective. Additionally, social media tools such as Facebook have also been useful for engaging the students and opening a venue for communication. Another method we have found useful is text messaging. We have found that students respond more quickly to text messages than to emails and telephone calls. We will utilize and build upon these methods to improve continued student tracking. These multiple tracking strategies will be used to update the table that is included in **Appendix D**, which lists the academic accomplishments of the Student Fellows.

**(f) Identify the number of scientific abstracts presented and peer-reviewed publications that result (Year 1, months 10-12)**

The Student Fellows gave a total of 9 scientific presentations, including two presentations at national scientific meetings. The mentors of the Student Fellows have confirmed that manuscripts that include some of the Student Fellows as co-authors are underway.

**Deliverables:** The Student Fellows are completing their sophomore and junior years of college and will apply to graduate or professional schools. The Student Fellows gave a total of 9 scientific presentations, two of which were made at two national scientific meetings. Also, each year, we ask the Student Fellows to evaluate the Training Program. The results from the 2012 Student Fellows are presented in the following table.

# SUMMARY RESULTS OF STUDENTS EVALUATIONS 2012 (n=7)

Survey Item	Strongly Disagree		Disagree		Not Sure		Agree		Strongly Agree	
	N	%	N	%	N	%	N	%	N	%
1. Overall, the summer program was a good research experience.	0	0.0	0	0.0	0	0.0	2	29%	5	71%
2. The summer program helped me learn the fundamentals of breast and prostate cancer and research.	0	0.0	0	0.0	0	0.0	2	29%	5	71%
3. The Princeton Review Graduate Record Examination (GRE) Course was effective in helping me to learn GRE test preparation strategies.	0	0.0	0	0.0	0	0.0	2	29%	5	71%
4. The seminar schedule was convenient.	0	0.0	0	0.0	0	0.0	4	57%	3	43%
5. The seminar topics were of interest to me.	0	0.0	1	14%	1	14%	3	43%	2	29%
6. Participating in the program helped to strengthen my desire for a career in cancer research.	1		1	14%	1	14%	3	43%	1	14%
7. The Program Director (Dr. Ford) was accessible and assisted me when needed.	0	0.0	0	0.0	0	0.0	2	29%	5	71%
8. The Program Assistant (Ms. Hazelton) was accessible and assisted me when needed.	0	0.0	0	0.0	0	0.0	0	0.0	7	100%
9. My research mentor was accessible and assisted me when needed.	0	0.0	0	0.0	0	0.0	3	43%	4	57%
10. I would recommend this program to other students at my college/university.	0	0.0	0	0.0	0	0.0	1	14%	6	86%

## REPORTABLE OUTCOMES

### **Student Summer Research Summaries**

Each Student Fellow prepared a research paper and gave a scientific presentation to their peers, mentors and other faculty at MUSC. Details regarding the manuscripts and scientific presentations developed by the Student Fellows are included in **Appendix A**.

## **CONCLUSIONS**

During the past year of funding of the DOD South Carolina Collaborative Undergraduate HBCU Student Summer Training Program, the tasks outlined in the Statement of Work were successfully met. Twelve Student Fellows were recruited from Claflin University, SC State University, and Voorhees College. Each Student Fellow conducted research and prepared a research paper that was presented at the conclusion of the program. The Student Fellows also presented their work at national conferences and were included as co-authors on peer-reviewed scientific publications, based on their summer research.

As shown in the following tables, two additional students participated in the DOD South Carolina Collaborative Undergraduate HBCU Student Summer Training Program using funds leveraged from another DOD grant that was funded in 2010 (DOD Grant Number W81XWH-10-2-0057, Southeastern Virtual Institute for Health Equity and Wellness). The DOD SE VIEW grant provided funding for two additional students per year beginning in 2010.

## 2010 DOD SE VIEW Grant Funded Students

Name		Mentor		
Janielle Samuel	Voorhees College	Dr. Marvella E. Ford	Testing protein glutathionylation levels In MCF7 breast cancer cells expressing glutathione S-transferase Pi Isoforms	GSTpi has been implicated in the forward reaction of S-glutathionylation. Therefore, we are interested in understanding how polymorphism may alter cellular responses for both oxidative and nitrosative stress. As such, the four alleles of GSTpi have been transfected into MCF7 breast cancer cells and we are testing the rate and extend the S-Glutathionylation via western blot analysis.
Edward McMorris	Voorhees College	Dr. Christina Voelkel-Johnson	Acid ceramidase overexpression and its role in the activation of and addiction to Akt signaling in prostate cancer	Previous studies have demonstrated the role of the ceramide metabolizing enzyme acid ceramidase in promoting an aggressive cancer phenotype in prostate cancer cell lines. In addition, it has been found that greater than 80% of prostate tumors overexpress acid ceramidase, suggesting that acid ceramidase may be an important mediator of development and progression of prostate cancer. In this study, we demonstrate that the increased rate of proliferation in acid ceramidase overexpressing cells is dependent on signaling through the oncogenic PI3K/Akt pathway. In addition, we found that acid ceramidase overexpressing cells are more sensitive to Akt inhibition than control cells, suggesting that acid ceramidase overexpressing tumors are addicted to Akt signaling. These findings highlight the importance of investigating the Akt pathway as a potential therapeutic target in acid ceramidase overexpressing tumors.

**2011 DOD SE VIEW Grant Funded Students (Continued)**

<b>Student's Name</b>	<b>Institution</b>	<b>MUSC Research Mentor</b>	<b>Research Title</b>	<b>Research Summary</b>
CoDanielle Green	SC State University	Dr. Marvella E. Ford	Evaluating an intervention to increase cancer knowledge in racially diverse communities in South Carolina; as well as, the increase in cancer knowledge's effect on cancer prevention activities.	To conduct a cancer education intervention with racially diverse communities in South Carolina. Then, to assess the impact that the cancer knowledge intervention is having on the cancer prevention activities of the residents.
De' Angelo Dinkins	SC State University	Dr. Christina Voelkel-Johnson	Thioredoxin 1 as a Therapeutic Target in Advanced Prostate Cancer	Prostate cancer is the 2nd leading cancer in men after lung cancer. Indolent disease can be treated fairly well and progresses slowly. However, the more aggressive form of prostate cancer spreads though out the body and there are no curative treatments. We tested the hypothesis that increased expression of redox proteins is an underlying cause for the aggressive, therapy-resistant prostate cancer phenotype. In our project we looked at the expression of redox proteins and susceptibility to chemotherapy in ARCaPe and ARCaPm cells.



## **2012 Annual Report Appendices**

## **Appendix A: Ernest E. Just Symposium Agenda**



# THE 2012 ERNEST E. JUST SYMPOSIUM FEBRUARY 24, 2012 DRUG DISCOVERY AUDITORIUM

WWW.MUSC.EDU/GRAD/JUST/



## Part I: Introduction

8:00 - 9:00

**Registration and Breakfast**

9:00 - 9:10

### Opening

Stephen Lanier, Ph.D., Associate Provost for Research  
Professor of Pharmacology, MUSC  
Etta D. Pisano, M.D. Dean, College of Medicine  
Vice President for Medical Affairs, MUSC

### Greeting

Sabra Slaughter, Ph.D., Chief of Staff  
Office of the President, MUSC



9:15 - 9:40

### *"The Biology of Just the Cell Surface-then and now"*

Gary Wessel, Ph.D.  
Professor of Biology and Medicine  
Department of Molecular and Cellular Biology & Biochemistry  
Brown University

## Part II: Role Models



9:45 - 10:10

### *"Career Path and Research in Stem Cell Tissue Engineering"*

Treena Livingston Arinze, Ph.D.  
Professor of Biomedical Engineering  
New Jersey Institute of Technology

10:15 - 10:30

**BREAK**

## Part III: Science



10:35 - 11:15

### **Ernest E. Just Symposium Keynote Speaker**

#### *"Implementation Science in Surgery"*

Selwyn O. Rogers Jr., M.D., M.P.H.  
Associate Professor of Surgery  
Division Chief, Trauma, Burn & Surgical Critical Care  
Brigham and Women's Hospital



11:20 - 11:35

#### *"Lupus: An Independent Risk Factor for Endothelial Dysfunction"*

Joy N. Jones Buie  
Ph.D. Candidate  
Medical University of South Carolina

11:35 - 12:20

### Breakout Sessions

Campus tour for visiting students  
Undergraduate Advisors meet with MUSC  
College Admissions Officers

12:25 - 12:55

**Lunch**

(Afternoon sessions are in the Bioengineering Building Rm 112)



1:00 - 1:50

#### *"Matrix Regulation of Lung Inflammation and Fibrosis: Lessons from Mouse and Man"*

Paul Noble, M.D.  
Professor of Medicine  
Chief, Division of Pulmonary, Allergy and Critical Care Medicine  
Duke School of Medicine



2:00 - 2:50

#### *"Enhancing Mammalian Regeneration"*

Nadia Rosenthal, Ph.D.  
Professor of Medicine  
Head of Outstation and Senior Scientist  
Adriano Buzzati-Traverso



3:00 - 3:50

#### *"Pluripotency, Etc, The Biomedical Promise of Stem Cell"*

Ihor Lemischka, Ph.D.  
Professor of Development and Regenerative Biology  
Professor of Pharmacology and Systems Therapeutics  
Director of The Black Family Stem Cell Institute  
Mount Sinai School of Medicine

**Appendix B: Ernest E Just Symposium Student Attendees from Claflin University, SC State University, and Voorhees College**

<b>Name of School</b>	<b># Students Who Participated in the 2012 Just Symposium</b>
<b>Claflin University</b>	<b>30</b>
<b>South Carolina State University</b>	<b>25</b>
<b>Voorhees College</b>	<b>11</b>

## **Appendix C: Summaries of Students' Scientific Research from the 2012 Summer Research Program**

Myshayla D. Bell

xCT Expression in Malignant Melanoma and Normal Skin Tissue

Dr. Shikhar Mehrotra

## Abstract

Melanoma is a malignant tumor of the melanocytes. Melanocytes are cells that produce a dark pigment called melanin, which is responsible for the color of the skin. Melanoma can occur in any part of the body that contains melanocytes. It is less common than any other skin cancer; however, it is the most dangerous if not detected early. It causes majority (75%) of deaths related to skin cancer. Melanoma is more common in women than in men; in women the melanoma site appears more on the legs and in men the site occurs on the back. There are a few treatments to cure or slow down the cancer. These treatments include: chemotherapy, immunotherapy, radiation, and/ or surgery. Chemotherapeutic agents are used to kill cancer cells. It is usually given if the melanoma has returned or spread. An example of a chemotherapeutic agent is Dacarbazine (DTIC). Immunotherapy is used to help your immune system fight the cancer. Examples of immunotherapy include interleukins, Interferon, or Cytokines. Radiation treatments may be used to relieve pain or discomfort caused by cancer that has spread. Surgery is another option to slow down the cancer that has spread to other parts of the body. If the melanoma found early, while it is still small and thin, and if it's completely removed the chances are high.

xCT is a glutamate/ cystine transporter that allows the cells to bypass the G1 / S arrest in the cell cycle. xCT carries out the rate of controlling the step of glutathione synthesis in cells. Also xCT is responsible for the uptake of cysteine in exchange for glutamate in most human cancer cells. The cystine/glutamate transporter consists of two components, the light chain and the heavy chain; another name for the light chain is xCT and another name for the heavy chain is CD98. The hypothesis is that xCT is overexpressed in the tumor cells and the neighboring T regulatory cells in human melanoma as compared to normal skin tissues. In the immune system, when something that is foreign attacks your body the T effector cells comes in to kill disease; but whenever a tumor is formed the T regulatory cells act as suppressor cells by regulating the T effector cells. This allows the tumor to proliferate and one possible reason is through overexpression of xCT allowing cancer cells to proliferate. xCT has been shown to be significant in the proliferation and multidrug resistance of cancer cells. Therefore, we would like to test our hypothesis that tumor cells promote the progression by allowing both tumor cells and the Treg cells to survive in the tumor environment. The proliferation of the Treg cells in the tumor environment will then allow the tumor to evade the immune system.

# xCT Expression in Malignant Melanoma and Normal Skin Tissue

Myshayla D. Bell  
Dr. Shikhar Mehrotra  
SURP Program



# Overview

- Melanoma
- xCT
- Immunohistochemistry
- Hypothesis
- Methods
- Experiments Tissue Micro Array
- Results
- Discussion
- Conclusion
- Acknowledgements

# Melanoma

- Melanoma is a malignant tumor of the melanocytes. Melanocytes are cells that produce a dark pigment called melanin, which is responsible for the color of the skin.

# What is xCT?

- xCT is a glutamate/ cystine transporter that allows cells to bypass the G<sub>1</sub>/S arrest in the cell cycle.
  - Glutamate: common amino acid that has an essential role in cellular metabolism.
  - Cystine: amino acid that is involved in building proteins and controls cellular function by catalyzing most chemical reactions.

# Immunohistochemistry

- Immunohistochemistry is the process of detecting antigens in tissue sections by the use of labeled antibodies through antigen-antibody interactions that are visualized by a marker such as fluorescent dye.

## General Overview of the Process

- Day 1: Block any non-specific binding of the primary antibody
- Day 2: Add Primary antibody
- Day 3: Add Secondary antibody

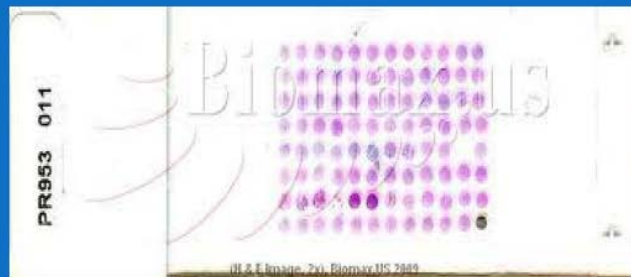
# Hypothesis

- Our hypothesis is that xCT is overexpressed in both the tumor cells in metastatic melanoma as compared to normal skin tissue.

# Experiments

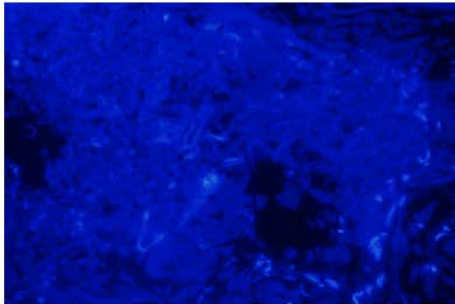
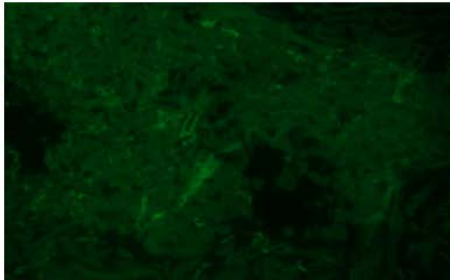
- Experiments 1 through 4 were all performed to set up the Tissue Micro Array in Experiments 5 and 6 and to learn the technique of IHC.

# Tissue Micro Array Display

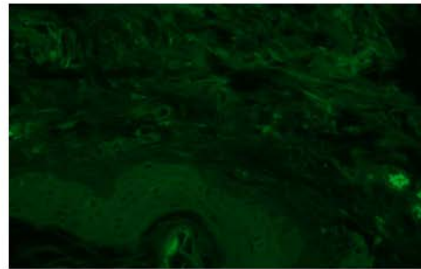


# Results Expt 005 ( Slide 5)

**Normal Skin Tissue**



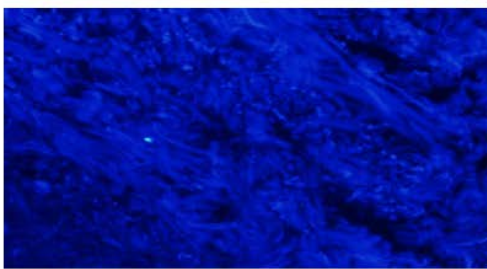
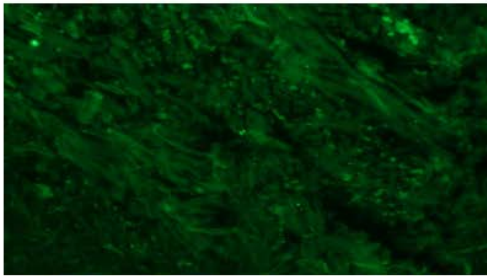
**Malignant Melanoma Stage 4**



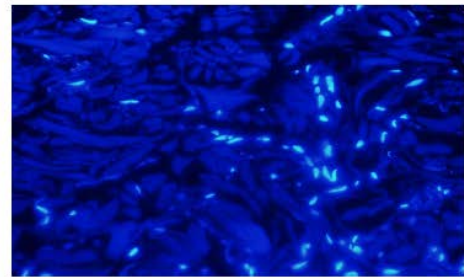
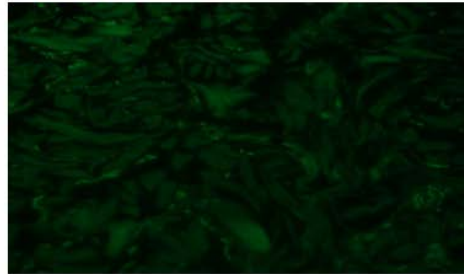


# Results Expt 005 (Slide 6)

**Malignant Melanoma of  
Rectum Stage 4**

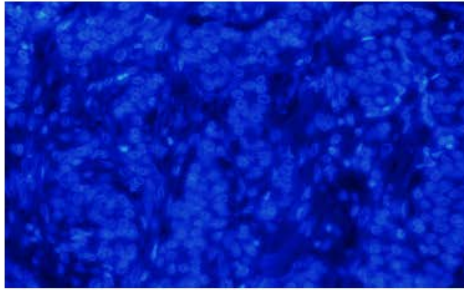
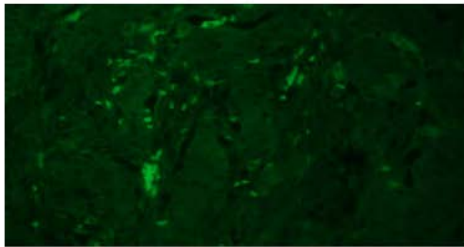


**Normal Skin Tissue of  
Rectum**

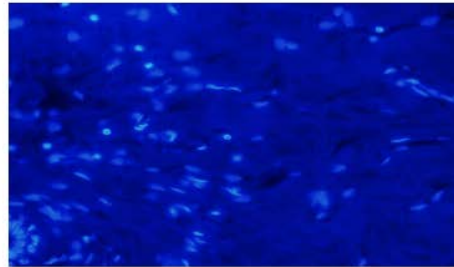
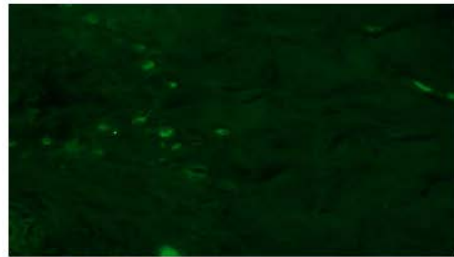


# Results Expt 006 (Slide 2)

Invasive Ductal Carcinoma  
of Breast Stage 2B



Normal Breast Tissue



# Discussion

- Based on the results shown, xCT is overexpressed in the tumor tissues compared to non-cancerous tissues. Non- cancerous tissues will show some expression of xCT, but the slides that were malignant were overexpressed with xCT.

# Conclusion

- The purpose of this experiment was to recognize if xCT was overexpressed in malignant tumor tissues compared to non- malignant tissues using Indirect Immunofluorescence microscopy.
- We also know that the negative control did show some xCT expression within the cells, but the tissues that were cancerous showed that the cells were overexpressed with xCT.

# Acknowledgements

- Dr. Shikhar Mehrotra
- Dr. Anuradha Murali
- Dr. Marvella Ford
- Hollings Cancer Center

## **IRS 1 Modulation of the DNA Repair Protein RAD51 in Breast Cancer**

Jasmine Fox, South Carolina State University

Dr. Erika T. Brown, Ph.D., Mentor

2012 MUSC Summer Undergraduate Research Program (SURP)

### **Abstract**

An appreciable number of African-American women are diagnosed with both breast cancer and metabolic syndrome (such as Type I/Type II diabetes). And, it is imperative to determine the molecular basis for this correlation. Moreover, African-American (AA) women are disproportionately diagnosed with Triple Negative Breast Tumors (TNBTs) (cells lack expression of estrogen, progesterone and Her2 receptors) at a significantly higher rate than Caucasian (CA) women. Approximately 25% of AA women diagnosed with breast cancer will have the TNBT classification, compared to only 11% of Caucasians (CA). The focus of this study was to determine the role of the DNA repair protein RAD51 in TNBT progression and in the relationship between breast cancer and metabolic syndrome. TNBT tumors generally express mutated BRCA1, which mediates the ability of RAD51 to effectively repair double-strand DNA breaks. Furthermore, IRS 1 (insulin receptor substrate 1) in the IGF (Insulin Growth Factor) insulin signaling pathway attenuates the nuclear translocation of RAD51 into the nucleus to repair damaged DNA—and BRCA1 regulates the transcription of IRS 1. Therefore, RAD51 appears to be the common protein in the breast cancer and metabolic syndrome pathways and deregulation of RAD51 may contribute to the dual diagnosis of both conditions. In the study, we have quantified IRS 1 expression and activity, and its effect on RAD51 expression and DNA repair activity in breast cancer cell lines mimicking TNBT status and having mutated BRCA1. These observations have been performed before and after induction of DNA damage. The preliminary results imply that mutated BRCA1 and estrogen receptor negative cells have inefficient DNA repair, which has known implications on cancer progression, but may also influence metabolic syndrome. Therefore, RAD51 could potentially be the common protein linking the dual diagnosis of both breast cancer and metabolic syndrome.





# IRS 1 MODULATION OF THE DNA REPAIR PROTEIN RAD51 IN BREAST CANCER

Jasmine Fox

South Carolina State University

Mentor: Erika T. Brown, Ph.D.

Department of Pathology & Laboratory Medicine

MUSC Summer Undergraduate Research Program (SURP)  
2012

## Breast Cancer Overview

- ▣ A group of diseases that cause cells in the body to change and grow out of control within the proximity of breast tissue
- ▣ About 1 in 8 women (just under 12%) will develop invasive breast cancer over the course of her lifetime



## BRCA 1 Gene and Protein Background

- ▣ Tumor Suppressor gene
- ▣ Associated with early-onset, familial breast cancer
- ▣ Works alongside BRCA2 protein to ensure the cell's DNA is stable
- ▣ Prevents uncontrolled cell proliferation and growth
- ▣ Regulates the DNA damage repair protein RAD51
- ▣ Mediates RAD51's activity by ensuring that it binds to the damaged DNA breakpoint after the region has been processed and prepared for repair

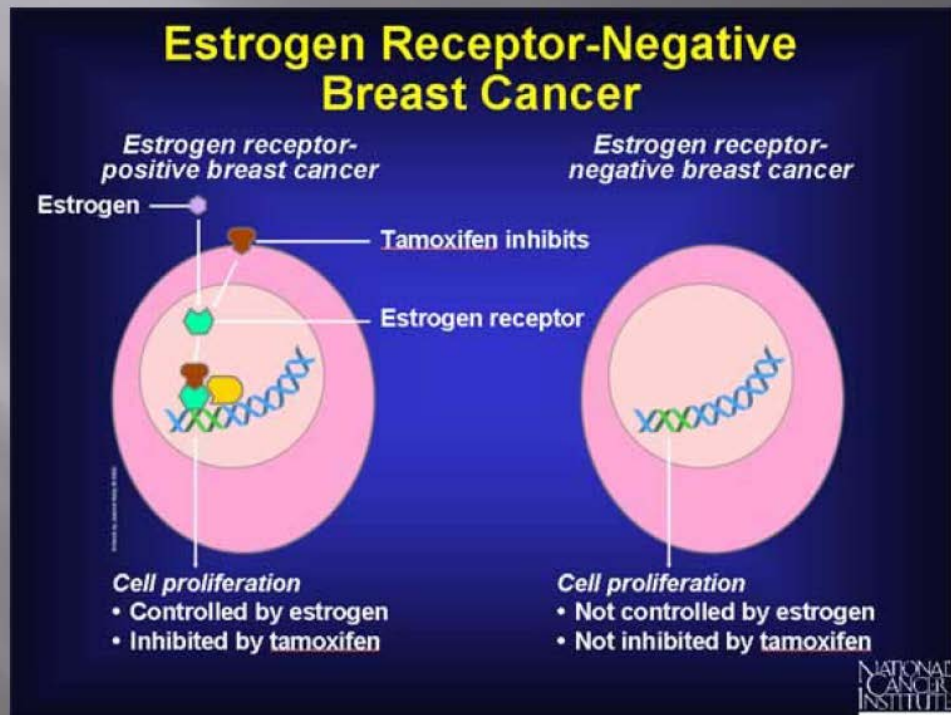
## Breast Cell Hormone Receptors

- ▣ Act as a messenger signal to the cell
- ▣ Receive signals from estrogen, progesterone, and HER2
- ▣ ER-estrogen and PR-progesterone enter the nucleus and regulate the expression of different genes
- ▣ HER2 receptor's function is to aide cell in growth and function
- ▣ They all cause breast cancer cells to grow and divide.
- ▣ Leading cause of Triple Negative Breast Tumors (TNBTs)

# Triple Negative Breast Tumors (TNBTs)

- ▣ A subset of breast cancers
- ▣ They do not express estrogen and progesterone receptors, also the HER2/neu receptor
- ▣ Unresponsive to commonly used hormone or receptor based treatments
- ▣ Tends to be higher among BRCA1 carriers

# Tamoxifen is ineffective in ER- /PR- and triple negative breast cancer



# RAD51 and IRS 1 Regulation

## *RAD51 is a DNA damage repair protein*

- ▣ A key player in maintenance of genomic integrity via homologous recombination (HR)
- ▣ RAD51 repairs double-strand DNA breaks

## *Insulin receptor substrate 1*

- ▣ It is a protein in the Insulin Growth Factor (IGF) pathway
- ▣ Its function is to mediate cell proliferation, migration, and survival
- ▣ IRS 1 can translocate to the nucleus and regulate gene transcription
- ▣ Phosphorylated IRS 1 binds RAD51 and is dephosphorylated after DNA damage, releasing RAD51 to facilitate DNA repair

# Homologous Recombination

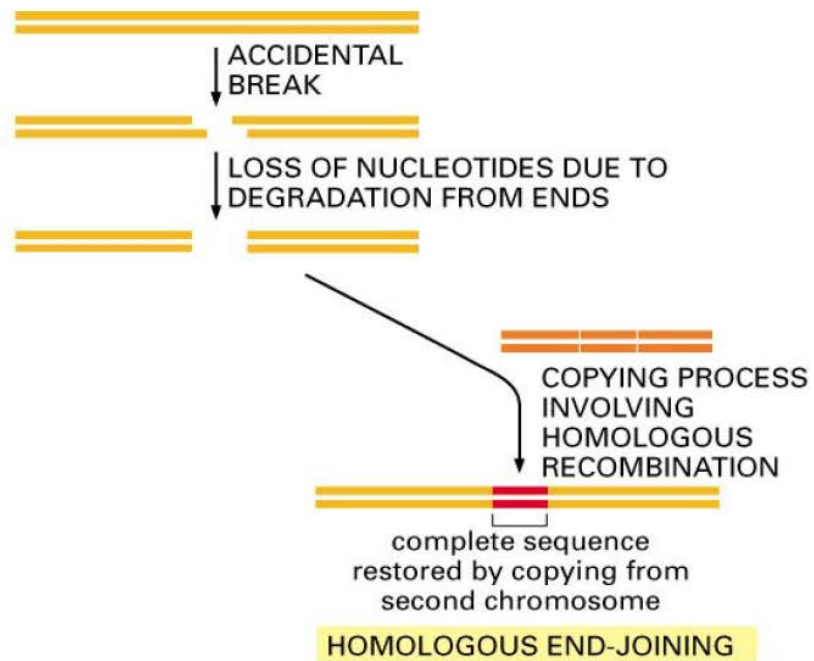


Figure 5-53. Molecular Biology of the Cell, 4th Edition.



## Metabolic Syndrome

- ▣ Insulin Resistance may increase risk for metabolic syndrome.
- ▣ *Not a disease.* A set of unhealthy risk factors:
  - High blood pressure, high blood sugar, unhealthy cholesterol levels, and abdominal fat.
  - Defined by presence of  $3 \geq$  risk factors.
- ▣ Is a precursor for Type II Diabetes.

## Why associate metabolic syndrome with breast cancer?

- ▣ Increasing evidence linking Type 2 Diabetes and various cancers
  - Insulin therapy increases cancer risk
  - Co-administered metformin, insulin sensitizer, decreases cancer risk associated with insulin
- ▣ Hyperinsulinemia could increase cancer incidence
  - Mechanisms unknown
  - Impaired signaling in the insulin/IGF pathway

*Chang et al, J Clin Endocrin Metab., July 2012, 97(7)*

*RAD51 may serve as the protein linking breast cancer progression and metabolic syndrome*



# Hypothesis

We hypothesize that deregulation of the DNA repair protein RAD51 may be the correlating factor in the association between the incidence of both breast cancer and metabolic syndrome, and that this occurs at the intersection of both the Insulin Growth Factor (IGF) signaling pathway and the DNA repair pathway.

## Specific Aims

- ▣ **Aim 1:** Quantify IRS 1 expression levels and phosphorylation under the control of normal (wildtype) and mutated BRCA1 in breast cancer cells
- ▣ **Aim 2:** Analyze the effect of IRS 1 under the control of normal (wildtype) and mutated BRCA 1 on RAD51 expression and DNA repair activity in breast cancer cells

## Cell Lines

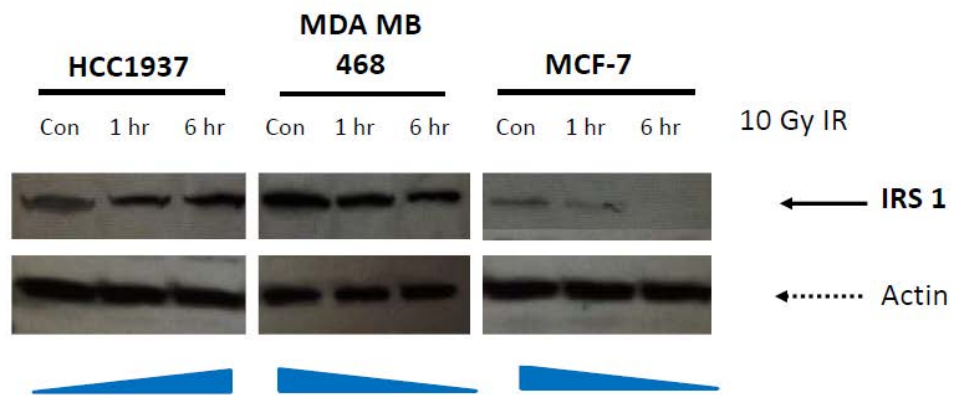
- ▣ Breast carcinoma cell lines
- ▣ Selected ER- and ER+ cells lines
- ▣ ER- cells; BRCA1<sup>+</sup> and BRCA1<sup>-</sup> status

Cell Line	Estrogen Receptor status	BRCA1 Status	BRCA1 mutation
HCC1937	-	-	5382delC
MDA-MB-468	-	+	
MCF-7	+	+	

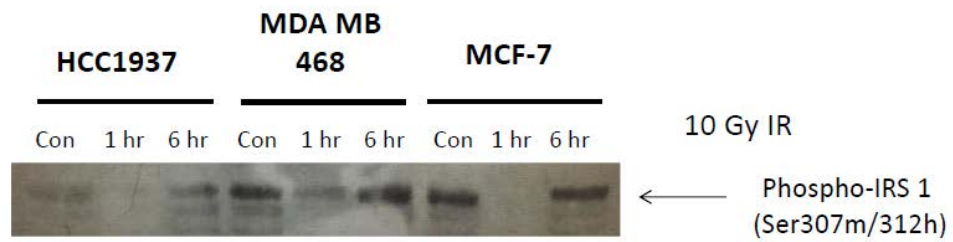
# Methodology

- ▣ Induce DNA damage using  $^{137}\text{Cs}$  irradiator source (10 Gy)
- ▣ Employ western blotting to assay changes:
  - IRS 1 expression and phosphorylation (Ser307)
  - RAD51 expression
- ▣ Analyze DNA repair by immunofluorescence for H2AX detection of double-strand DNA breaks

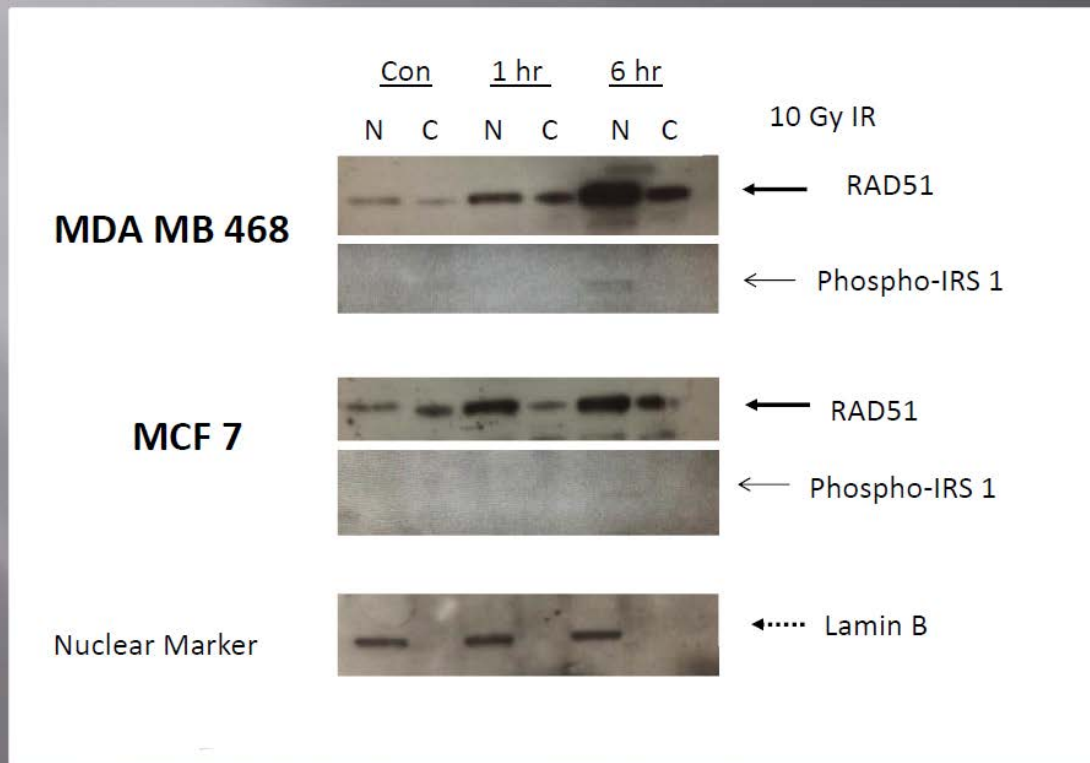
## IRS 1 levels increase in HCC1937 after DNA damage



## IRS 1 is dephosphorylated 1 hour after DNA damage



## Nuclear concentrations of RAD51 increase after DNA damage



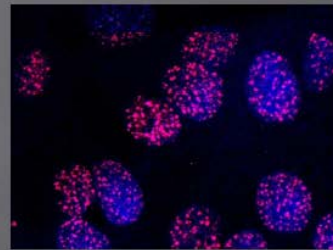
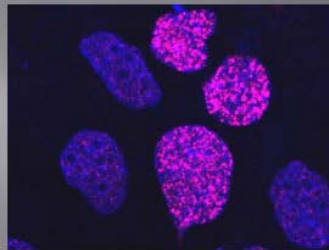
## Immunofluorescence detection of DSBs (g-H2AX)

1 hr Post-IR

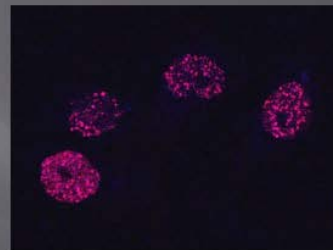
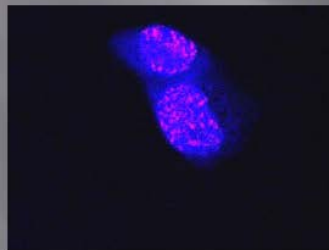
6 hrs Post-IR

10 Gy

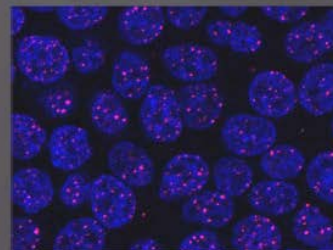
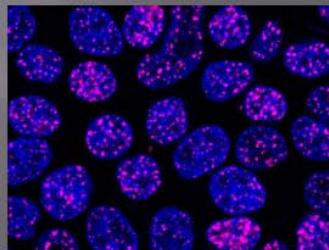
HCC1937  
(ER-; BRCA1-)



MDA MB 468  
(ER-; BRCA1+)

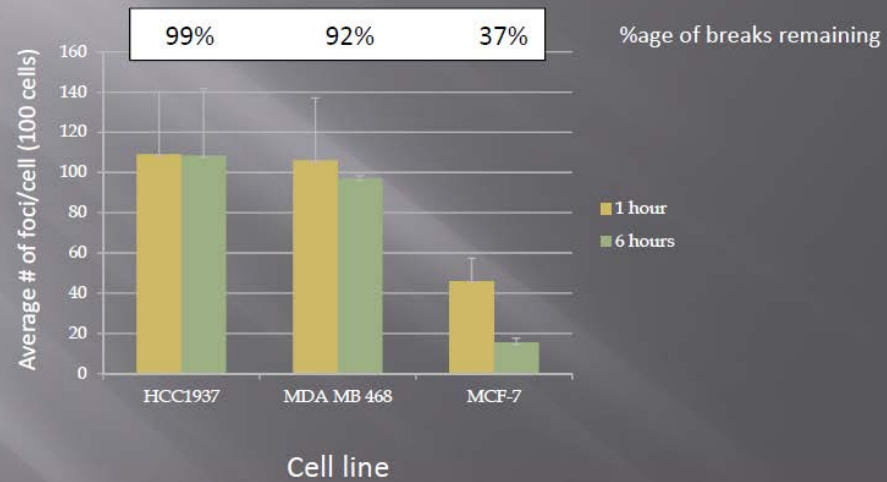


MCF-7  
(ER+; BRCA1+)





## Average number of foci per cell after DNA damage



## Summary

- ▣ IRS 1 levels increase after DNA damage in HCC1937 and decrease in MDA MB 468 and MCF 7
  - BRCA1 mutation (HCC1937) may cause difference in IRS 1 expression after DNA damage.
- ▣ De-phosphorylation (Ser307 mouse/Ser312 human) occurs 1 hour after DNA damage
- ▣ IRS 1 de-phosphorylation at 1 hour may indicate:
  - IRS 1 may assist in RAD51 nuclear translocation into the nucleus
  - IRS 1 may bind to RAD51 until the damaged DNA has been prepped and is ready for repair
- ▣ HCC1937 and MDA MB 468 cells (ER-) showed higher DNA damage and inefficient resolution of DSBs when compared with MCF-7 cells (ER+)
  - Imply that ER status is important for DNA repair
  - ER status also is important in allowing IRS 1 to enter the nucleus
  - These may explain the differences in DSB repair in the ER- vs. ER+ cell lines.

# Acknowledgements

- ▣ Erika T. Brown, Ph.D., Advisor
- ▣ Shweta Singh, Ph.D.
- ▣ Marvella Ford, Ph.D.
- ▣ MUSC's Summer Undergraduate Research Program (SURP)
- ▣ Hollings Cancer Center
- ▣ Department of Defense Research Grants Program

Targeting Protein Folding as  
a Therapeutic Strategy in Prostate Cancer

Claudia Thompson  
Danyelle Townsend, PhD

## Abstract

S-glutathionylation is the post translational modification of the protein cysteine and this modification is often triggered by oxidative and nitrosative stress on cells. Oxidative and nitrosative stress cause reactions that often time alter protein structures which in turn causes an interference of normal body functions. Protein disulfide isomerase (PDI) is the most abundant isomerase in the endoplasmic reticulum (ER) of cancer cells and it is very important for protein folding. When using targeted drug therapy the idea is to pick a target that is more abundant or only found in cancer cells, so PDI is an ideal target because of its abundance. PDI inhibitors are used as the target drug because they block PDI from doing its job in the cells. PDI inhibitors cause stress on the cells which causes the cysteine residues of PDI to be S-glutathionylated, which reduces isomerase activity. Without PDI assisting in the folding and unfolding of proteins there is an increase in the number of unfolded proteins and an activation of the unfolded protein response (UPR). The activation of UPR will then lead to UPR induced cell death, therefore killing the cancer cell. This mechanism is thought to work with all cancers including prostate cancer (PC), which is the topic of interest for my research. PC is one of the most common cancers in American men as the chance of having it increases with age. Despite its high rate of incidence PC has a rather low rate of mortality because most cases of PC are slow growing and not very aggressive. The PC-3 cells that were used in the study were collected from a bone metastasis of grade four cancer from a caucasian male 62 years of age. During the study we treated the PC-3 cells with two different PDI inhibitors (drugs), PABA/NO and PAO. We treated the cells with various concentrations of the two drugs and used MTT drug assays to determine the toxicity of the drugs and we also used western blots to detect the levels of PDI in the cells.

# Targeting Protein Folding as a Therapeutic Strategy in Prostate Cancer

Claudia Thompson  
Danyelle Townsend, PhD

# Prostate Cancer

- 1 in 6 men diagnosed annually
- Approximately 241,740 new cases
- Average age of diagnosis is 67 years old
- Approximately 28,170 men will die annually
- PC is the second leading cause of cancer death in American men

\*American Cancer Society



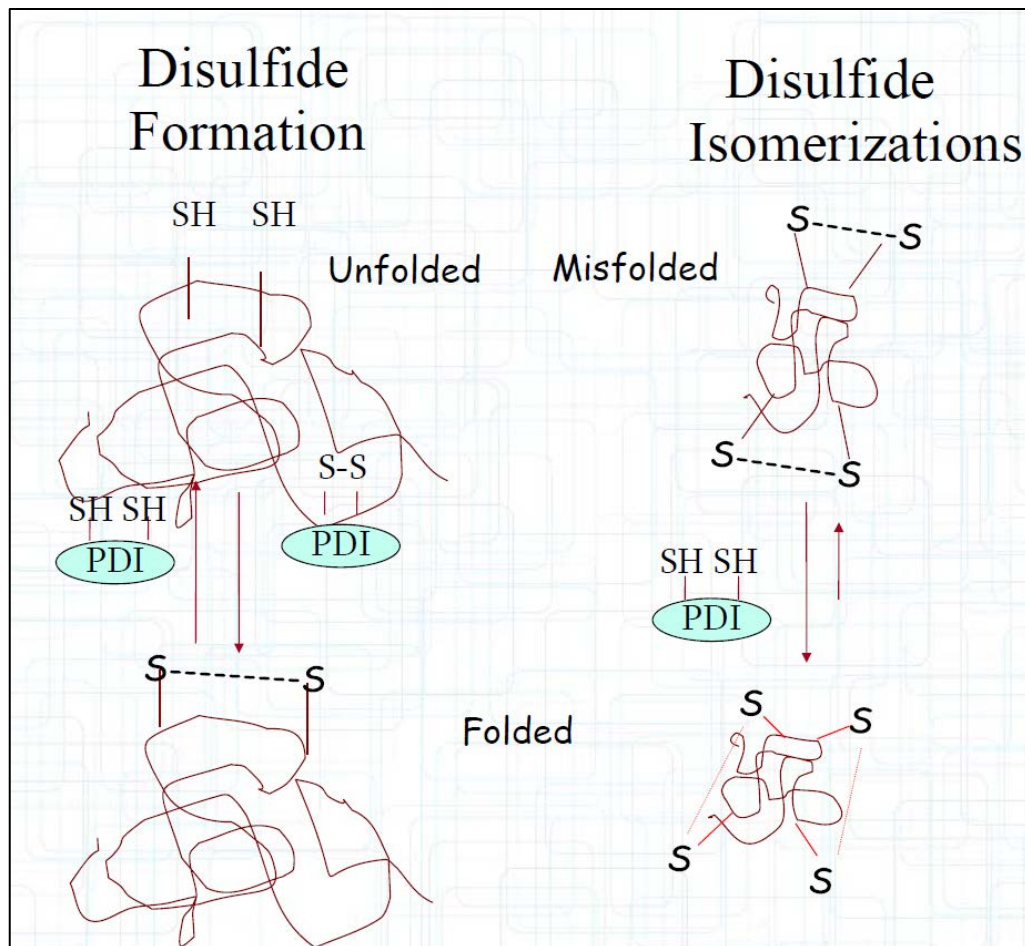
## Prostate Cancer Cells

Significance: Rapidly dividing cells have a high protein synthesis demand. Blunting protein folding is a unique drug treatment strategy to enhance therapeutic treatment plans.

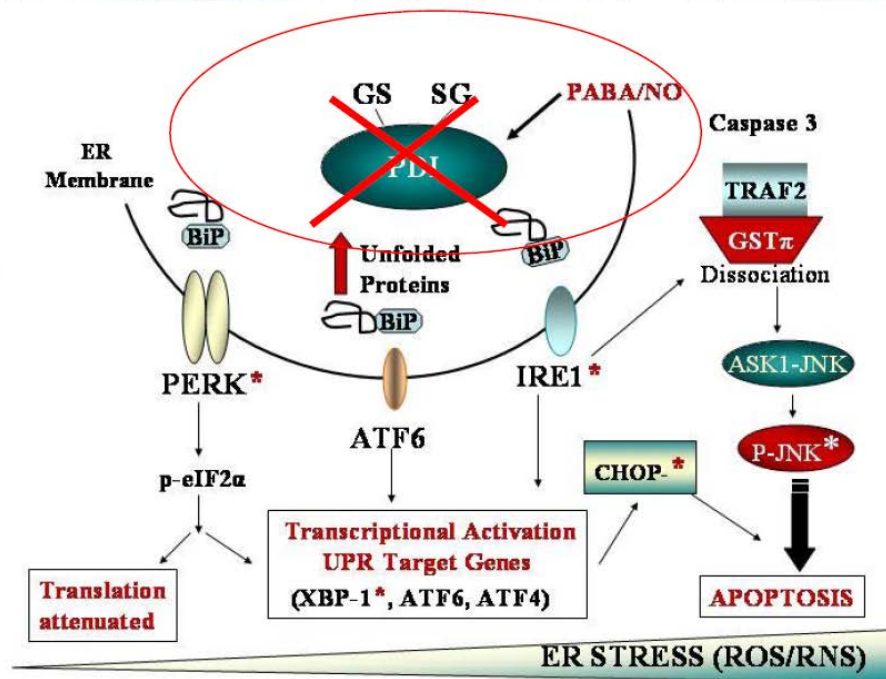
Rationale: Protein disulfide isomerase (PDI) is the most abundant chaperone in the ER.

- \* PDI is overexpressed in cancer
- \* Overexpression is concurrent with poor prognosis and clinical outcomes





# The Role of PDI in the Unfolded Protein Response



**Hypothesis:** Targeting PDI to blunt protein folding will be a novel treatment strategy.

**SPECIFIC AIMS:**

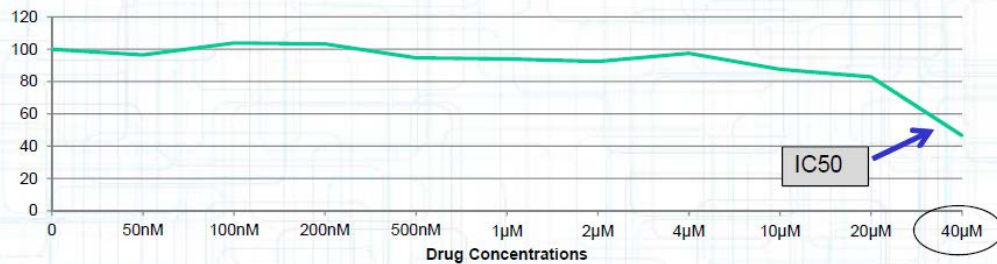
- Evaluate the toxicity of PDI inhibitors, PAO and PABA/NO, in PC-3 prostate cancer cells.
- Western blot analysis of PDI in PC-3 cells after IC50 (half maximal inhibitory concentration) treatment.

## Methods

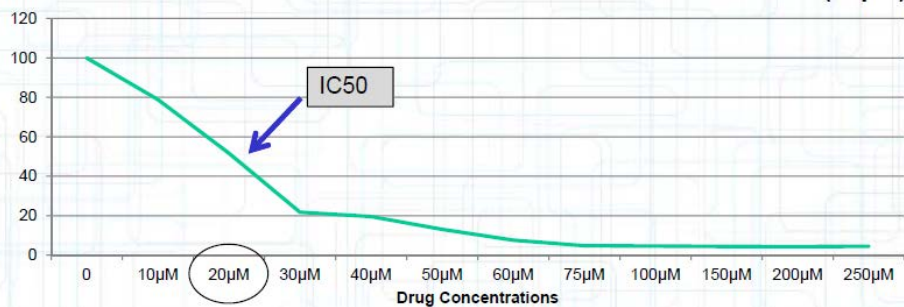
- Cell Culture
  - PC3 cell line – initiated from a bone metastasis of a grade IV prostatic cancer from a 62-year-old Caucasian male
- Cytotoxicity Assays
  - Survival curve determined by MTT assay
- Westernblot Analysis
  - Expression of PDI in PC-3 cell

# MTT Assay Testing PABA/NO toxicity

Percent Survival of PC-3 cells after PABA/NO Treatment (exp 1)



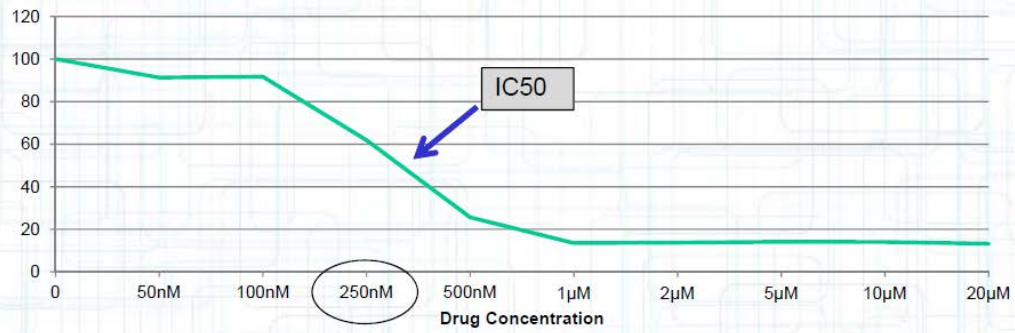
Percent Survival of PC-3 Cells after PABA/NO Treatment (exp 2)



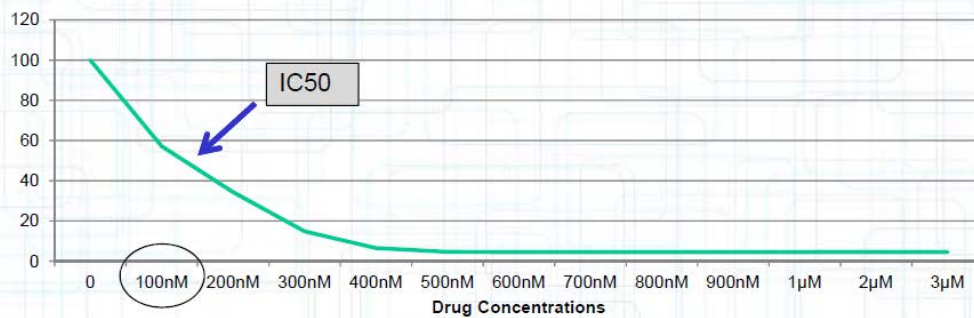


# MTT Assay Testing PAO toxicity

Percent Survival of PC-3 cells after PAO Treatment (exp 1)



Percent Survival of PC-3 cells after PAO Treatment (exp 2)



## Drug treatment effect on PDI expression in PC cells

Western  
Blot for  
PDI



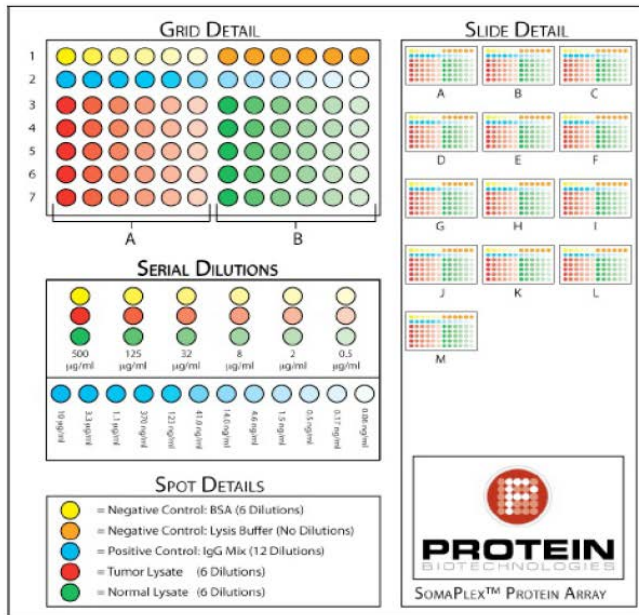
\*after 24 hour exposure

# Protein Array Analysis

## SOMAPLEX™ REVERSE PHASE PROTEIN MICROARRAY

HUMAN PROSTATE & TESTES TUMOR & NORMAL TISSUE

PMA3-001-N



**Objective:**  
Determine if PDI expression changes with prostate cancer progression, metastasis, or drug resistance



## Summary

PDI is over-expressed in cancer cells

PABA/NO and PAO elicit cell death (MTT analysis)

PABA/NO and PAO 24 hour treatment at IC50 concentrations did not decrease PDI expression in PC-3 cells (Western Blot analysis)

Protein array will be done in future experiments

# References

**-S-glutathionylation Indicator of Cell Stress and Regulator of the Unfolded Protein Response; Danyelle M. Townsend; Molecular Interventions December 2007 Vol 7, Issue 6**

**- S-Glutathionylation of Protein Disulfide Isomerase Regulates Estrogen Receptor  $\alpha$  Stability and Function; Ying Xiony, Yefim Manevich, Kenneth D. Tew, and Danyelle M. Townsend; Hindawi Publishing Corporation International Journal of Cell Biology Vol 2012, Article ID 273549, 9 pages doi: 10.1155/2012/273549**

# Acknowledgments

- Danyelle Townsend, PhD
- Marvella Ford, PhD
- Steven Hutchens
- Tew Lab



# **Cancer Epigenetics: Combining LSD1 and DNA methylation inhibitors for targeted breast cancer treatment**

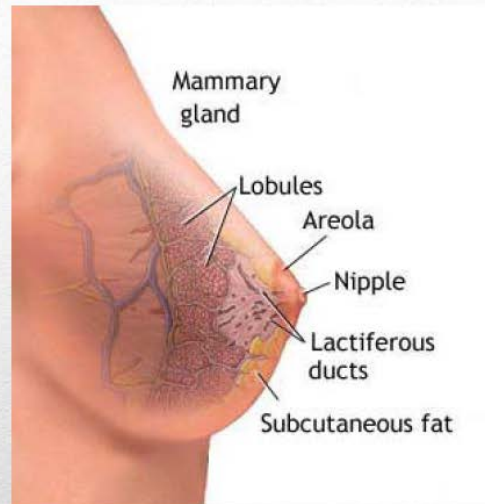
Britney White  
Biology major, Chemistry minor  
Claflin University

Patrick M. Woster, Ph.D.  
College of Pharmacy  
SCCP Pharmaceutical and Biological Sciences  
Drug Discovery Building  
Medical University of South Carolina

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Summer Undergraduate Research Program 2012

- What is Breast Cancer?
- Who gets Breast Cancer?
- Breast Cancer Treatment?

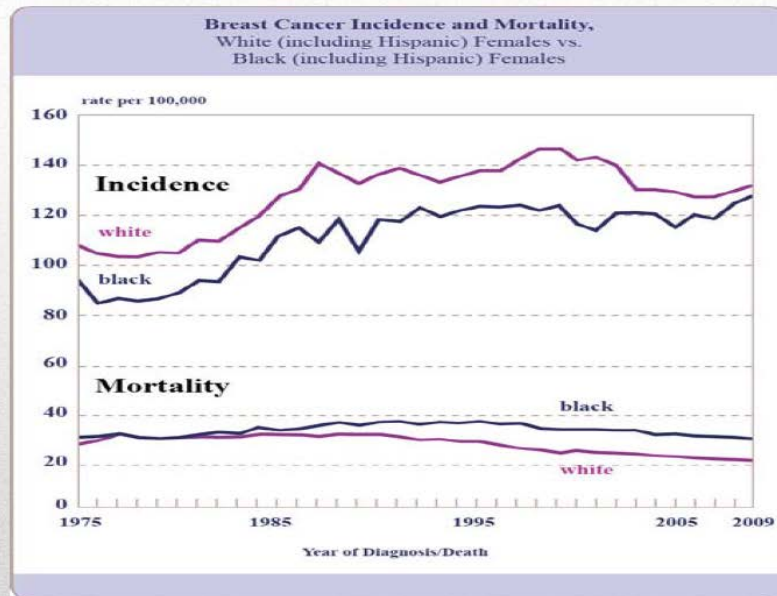


REKLAM 1

# Breast Cancer

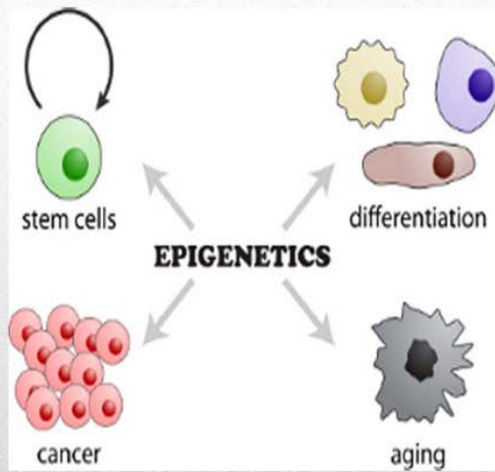
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\*Age-adjusted to the  
2000 U.S. standard  
population.  
Source: SEER Cancer  
Statistics Review,  
1975-2009, 2012

## BrCa Incidence and Mortality Rates



- This is the study of changes in gene expression outside of DNA modifications
- Examples include, DNA methylation and histone modification
- These modifications are proposed to be binding sites for protein recognition modules, such as methylated lysines
- The modification of these histones create an epigenetic mechanism for the regulation of normal and disease processes

# Epigenetics

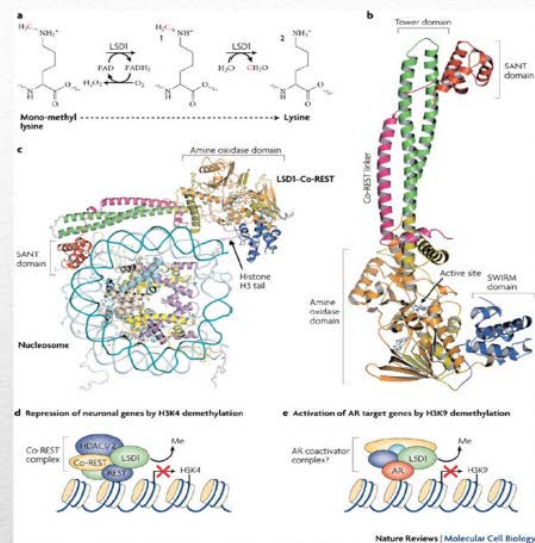
- Histone modifications disturb a particular gene that is important in tumor develop: the tumor suppressor genes
- Tumor suppressor genes are genes that protect the cell from a step in the path to cancer
- When expression is disturbed in these genes, it can cause problems in the cell which can eventually lead to cancer
- This gene modification causes it to be epigenetically silenced
- The modification in the histone turns these genes off

## **Tumor Suppressor Genes**

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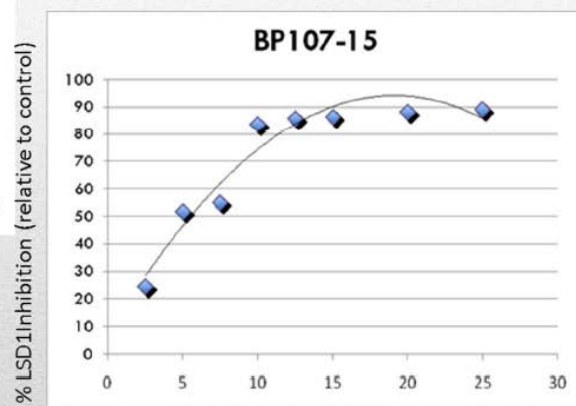
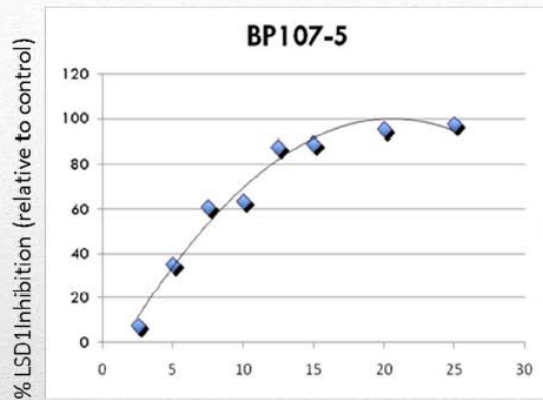


- Lysine specific demethylase 1, or LSD1 codes for a flavin-dependent monoamine oxidase
- This oxidase can demethylate mono- and dimethylated lysines
- Specifically, it removes histones from these methyl groups, H3K4 and H3K9
- This enzyme is important because it is known for silencing tumor suppressor genes
- LSD1 demethylates histone 3 lysine residues which results in the repression of genes involved in normal growth as well as cancer



# Lysine specific demethylase 1 (LSD1)





# Inhibitory Activity

- Based on all the background information, a proposal that the LSD1 inhibitors will decrease cancer cell growth in breast cancer tissue cells
- Also, based on the epigenetics, the introduction of a DNA methylation inhibitor in combination with the LSD1 inhibitor will yield a greater outcome in reducing cancer cell growth in the breast cancer cells
  - Cell adaption

## Hypothesis

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# Experiment

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- We used two different cell lines:
  - MCF7 (ER+)
  - MDA-MB-231 (ER-)
- 96 well plates
- 5,000 cells in each well
- Each cell line was distributed across two plates
- Two drugs were used for the experiment
  - The first drug was BP-107-15, an LSD1 inhibitor
  - The other drug was 5-Azacitidine, which is a DNA methylation inhibitor

## **Cell Lines and Drugs Used**

---

- Four treatments were given:
  - BP-107-15
  - 5-AC
  - BP-107-15 + 5-AC<sub>C1</sub>
  - BP-107-15 + 5-AC<sub>C2</sub>
- For the combination treatments, the first one was BP-107-15 with 1  $\mu$ M 5-AC and the second was BP-107-15 with 5  $\mu$ M 5-AC
- For each treatment there were 10 concentrations used
- Vehicle (control), 1, 2.5, 3.75, 5, 6.25, 7.5, 8.75, 10, and 11.25 $\mu$ M

## Treatments

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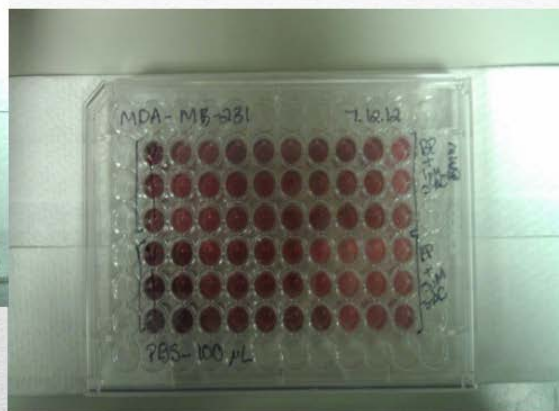
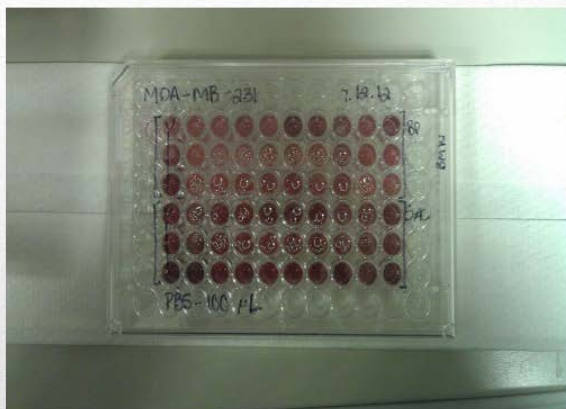




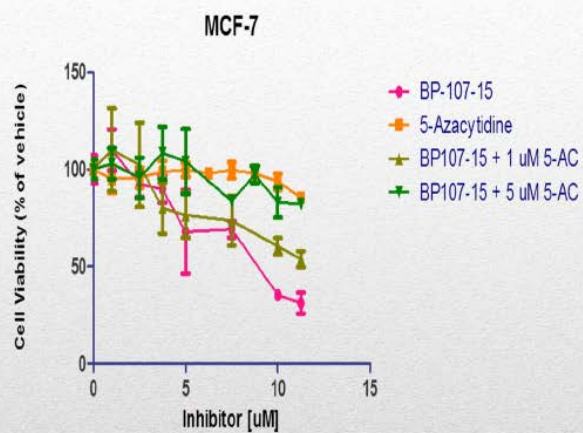
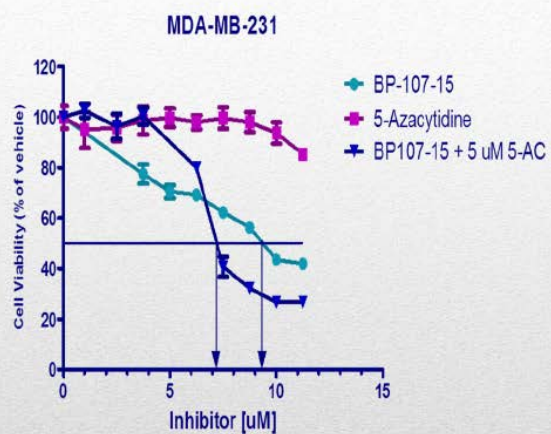
- For each cell line, 50  $\mu$ L of cells went into each of the 60 wells
- Next, 50  $\mu$ L of each drug treatment went in after the cells in each of the 60 wells for each drugs
- The plates stayed in the incubator and was observed over the course of 96 hours; after, the MTS reagent was added to obtain the color change
- The color change is to detect cell viability
- Increased purple coloring=increased amounts of cells
- Plate reading:
  - Absorbance at 490 nm was read on a plate reader
  - Values are relative to control (set to 100)

## MTS Assay

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## Data/Results



# Cell Viability

- Cell growth was inhibited in the presence of the LSD1 inhibitor, as well as in the DNA methylation inhibitor as well
- In the combination plates, specifically for the MDA-MB-231 cells, a great decrease was shown
- The MCF7 cells, however, did not have the same trend; there was a higher decrease in cell growth in the BP-107-15 drug alone versus the cells containing both drugs
  - There is little to no change in 5-AC aspect
- The results show us, also, that all cell lines are different
- MCF7 are ER+ and the MDA-MB-231 are ER-; in this case the results are great due to the fact the MDA-MB-231 cells are more tumorigenic

## Conclusion


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- Because inhibition was seen in the breast cancer cells with the combination of LSD1 and DNA methylation inhibitors, synergistic interaction will now be investigated
- Further tests are being performed

## **Future Work/Research**

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- 
- Dr. Patrick Woster
  - Melissa Sokolosky
  - Steve Holshouser
  - Dr. Marvella Ford
  - Ms. Tonya Hazelton
  - Drug Discovery Building and Staff
  - Summer Undergraduate Research Program 2012
  - Medical University of South Carolina

# **Acknowledgements**

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Sylvia Bridges

MicroRNA 377 levels are disparate in Prostate Cancer Patients.

### **Abstract**

Prostate cancer (PrCa) is cancer that starts in the prostate gland. The prostate is a small, walnut-sized structure that makes up part of a man's reproductive system. MicroRNAs (miRNAs) are a class of naturally occurring, small non-coding RNA molecules, about 21–25 nucleotides in length. Of interest to this study, misregulation of miRNAs have been associated with cancer progression and prediction. To assess whether miR-377 levels are disparate among men with prostate cancer, miR-377 levels were measured in matched tissue and serum samples from African American (AA) and Caucasian American (CA) men with low grade and high grade PrCa. First we extracted the RNA and then performed an RT reaction, which is a process in which RNA is reverse transcribed into complementary DNA. We next performed real time PCR to assess the levels of miR-377. The results showed that the levels of miR-377 are lower in serum from AA when compared to CA prostate cancer patients in both low grade and high grade samples.

Taken together, these data support the specific hypothesis that miRNA-377 levels are lower in African Americans (AA) than in Caucasian American (CA) prostate cancer patients and that this might be a mechanism of PrCa disparity. Furthermore, ETS-1 may be a direct target of miR-377 and therefore a potential mechanism of disparity in these patients.



# Disparities in MicroRNA 377 Levels in Prostate Cancer

Sylvia L. Bridges

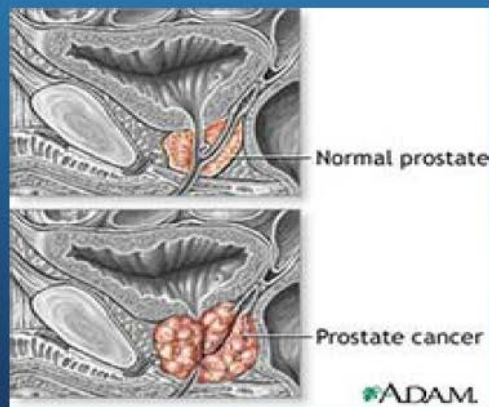
Mentor: Victoria J. Findlay, Ph.D.

Summer Undergraduate Research Program 2012



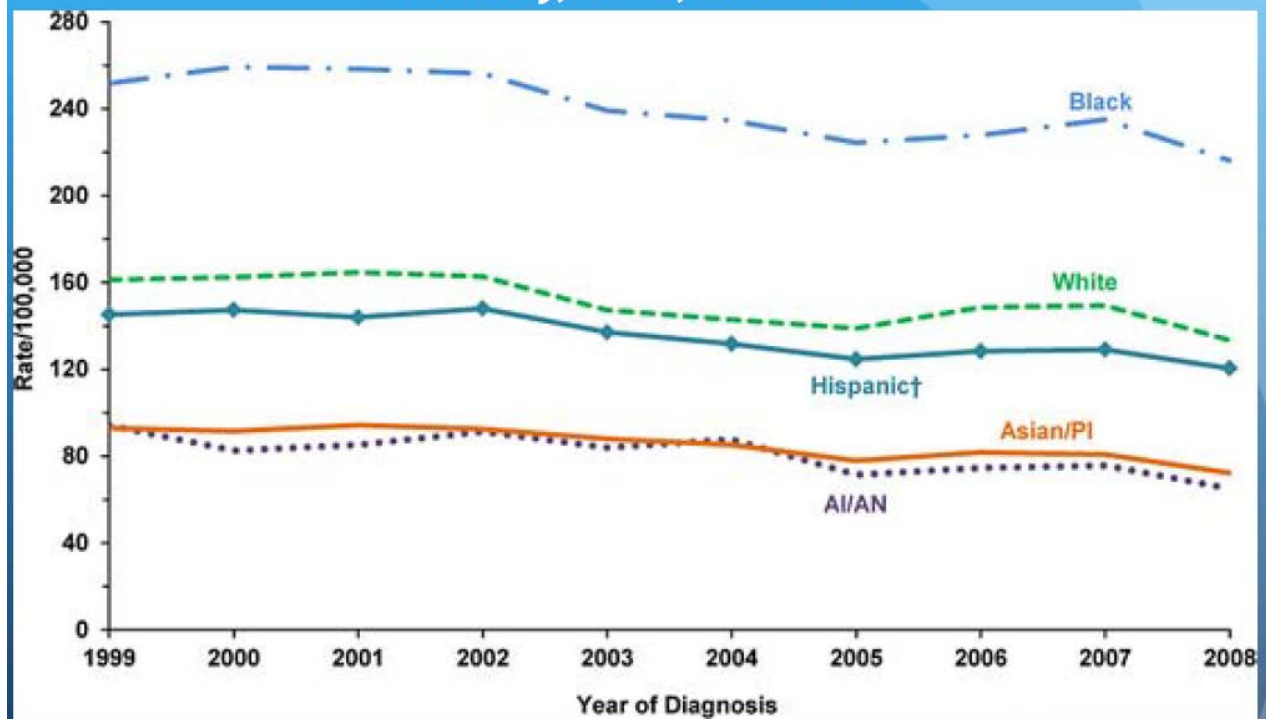
# What is Prostate Cancer?

- Prostate cancer (PrCa) is a form of cancer that develops in the prostate, a gland in the male reproductive system. Prostate cancer is the most common cause of death from cancer in men over age 75 years. People who are at higher risk are African American (AA) men, men who are older than 60 years, and men who have a father or brother with prostate cancer.



Source: BHR Pharma, LLC

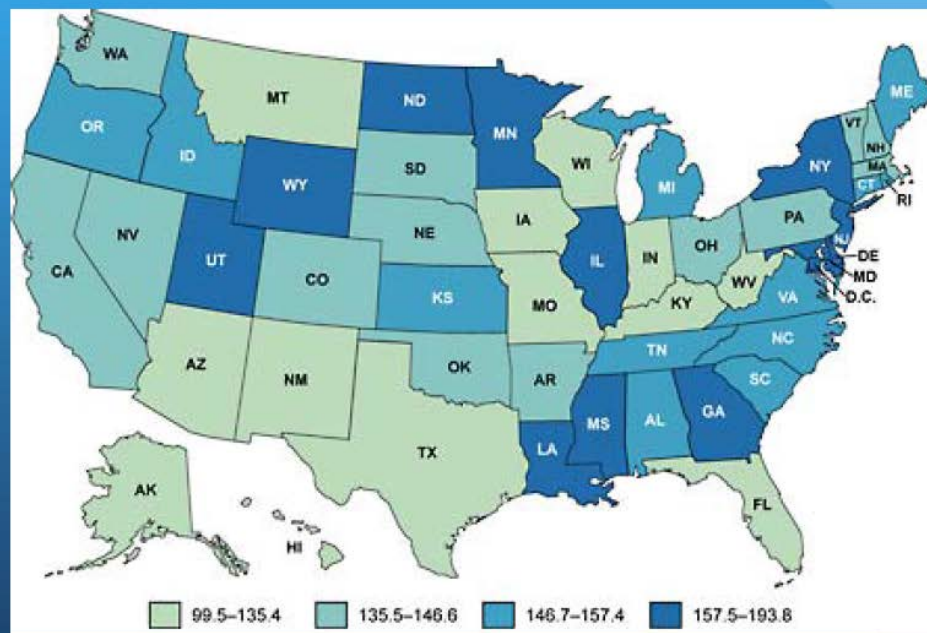
## Prostate Cancer Incidence Rates by Race and Ethnicity, U.S., 1999-2008



Source: Division of Cancer Prevention and Control

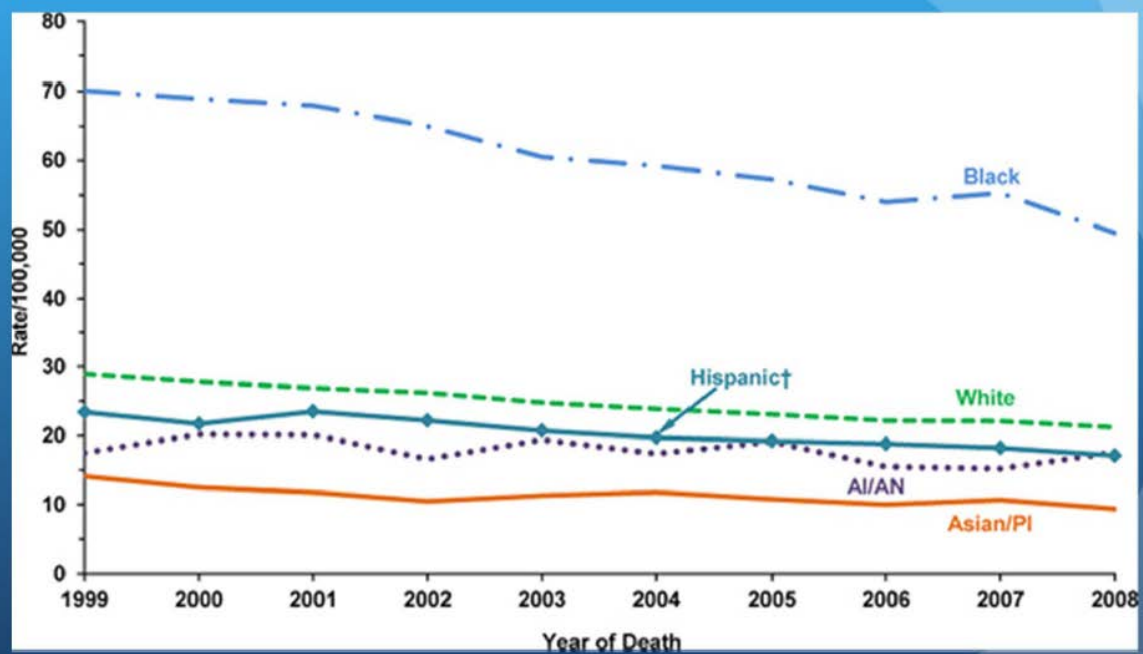
## Prostate Cancer Incidence Rates by State, 2008

Rates are per 100,000 and are age adjusted to the U.S. standard population.



Source: U.S. Cancer Statistics Working Group

## Prostate Cancer Death Rates by Race and Ethnicity, U.S., 1999-2008



Source: Division of Cancer Prevention and Control

# What are MicroRNAs?

- MicroRNAs (miRNAs) are a class of naturally occurring, small non-coding RNA molecules, about 21-25 nucleotides in length. Dysregulated miRNA levels have been associated with several cancers and more recently to be disparate in cancer. miR-377, the miRNA of interest in this study, is located on chromosome 14q23, a region shown to be altered in AA and European American (EA) prostate cancer patients.



## Background

- MicroRNAs work through the negative regulation of coding genes. The transcription factor ETS-1 is bioinformatically predicted to be a direct target of miR-377 and is known to be a positive regulator of prostate cancer progression.

# Hypothesis

- We hypothesize that miRNA-377 levels will be lower in AA than in EA prostate cancer patients and that this might be a mechanism of PrCa disparity. The hypothesis is based on lower levels of miR-377 that were detected in tumor samples from AAs with PrCa.
  - A published study reported lower levels of miR-377 in serum from AA breast cancer patients when compared to EA breast cancer patients.



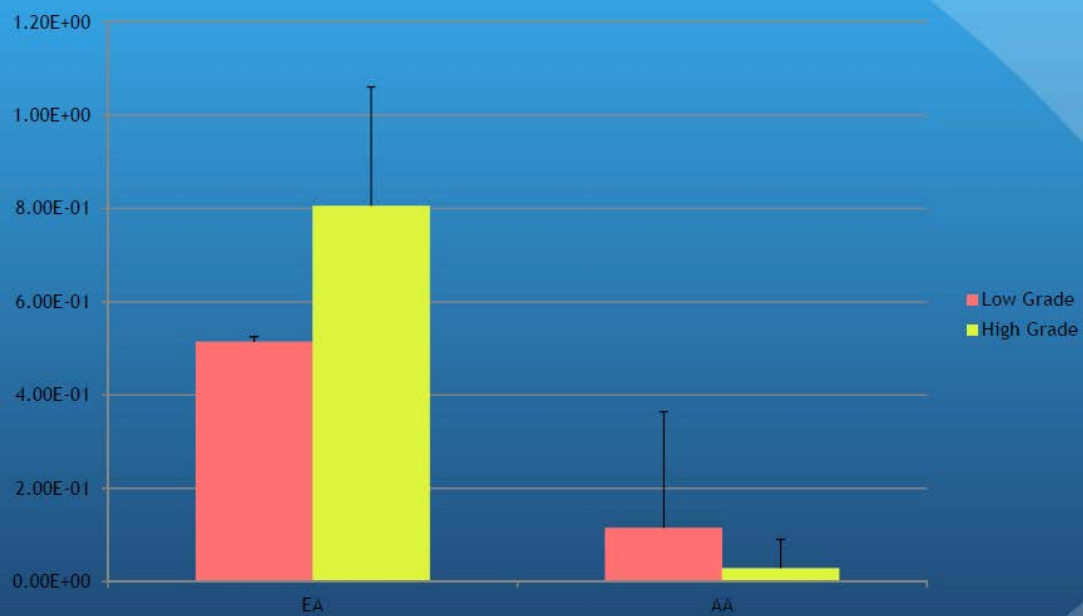
# Specific Aim 1

Assess miR-377 levels in serum samples from patients with low grade and high grade PrCa.

# Methods

- Use of Trizol LS Reagent to isolate high-quality total RNA
- Reverse Transcription (cDNA)
- Real Time Polymerase Chain Reaction (RT-PCR)

## miR-377 levels are lower in AA men with PrCa



Low Grade - Gleason 4-6; High Grade - Gleason 7-10

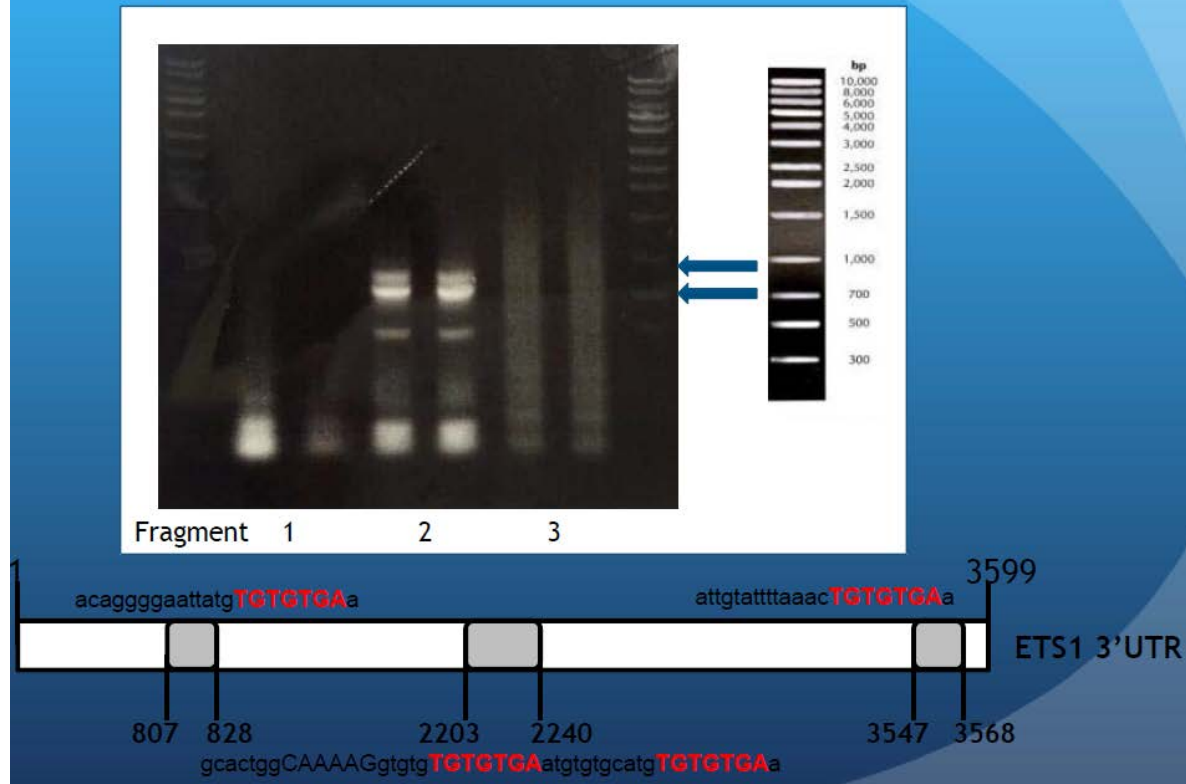
## Specific Aim 2

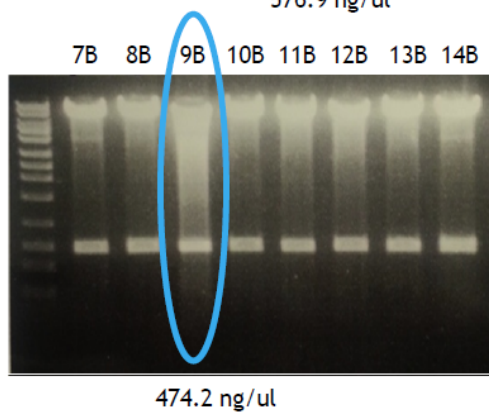
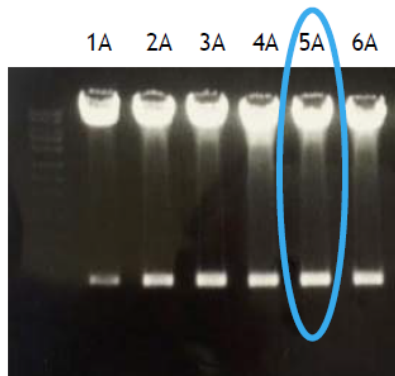
Determine if ETS-1 is a direct target of miR-377.

# Methods

- ThermalAce PCR
- Gel Electrophoresis
- Cloning
- QIAprep Spin Miniprep
- Transfection
- Luciferase Assay

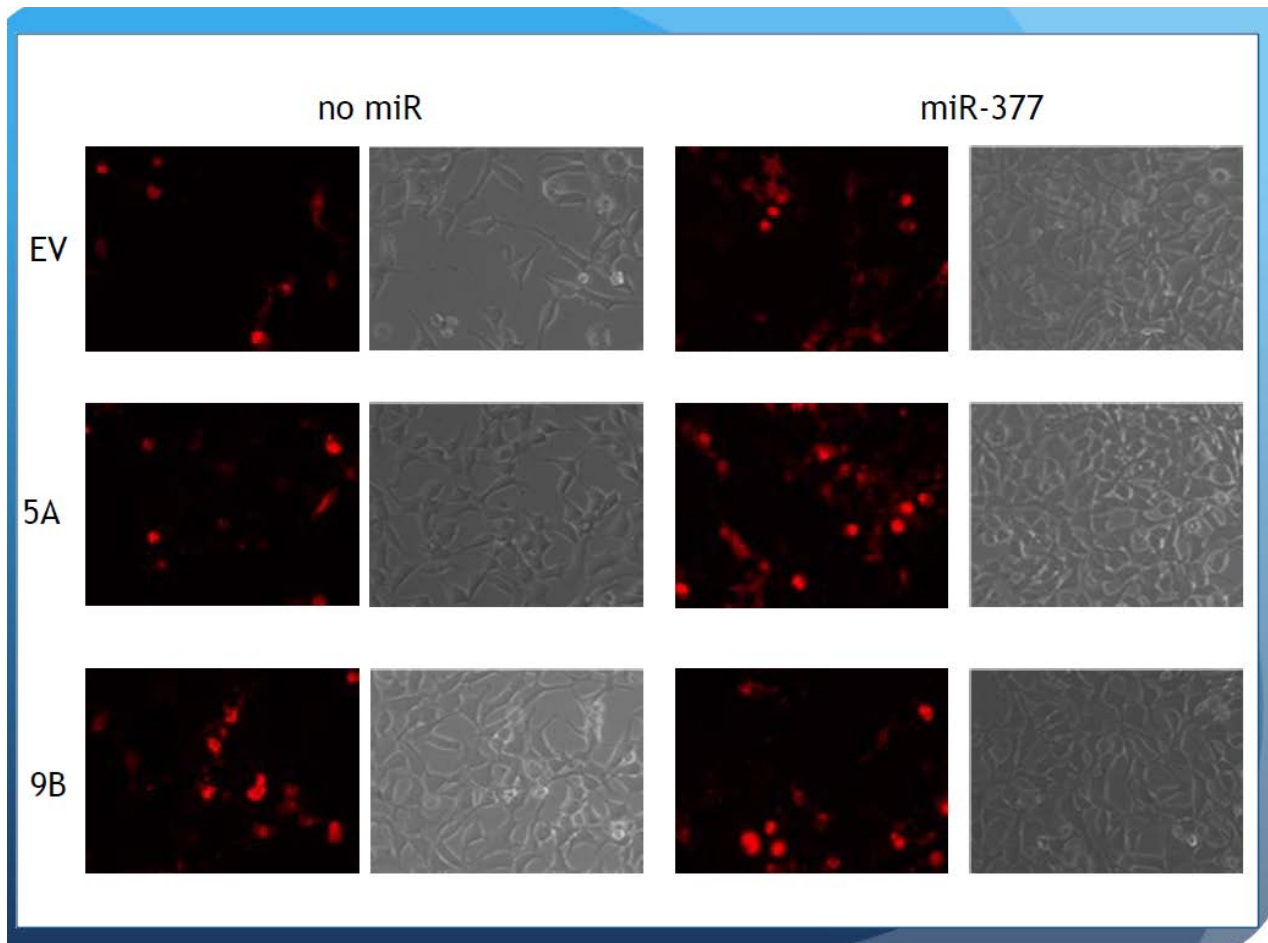
Fragments are expected to be seen at 988bp, 873bp, and 632bp.





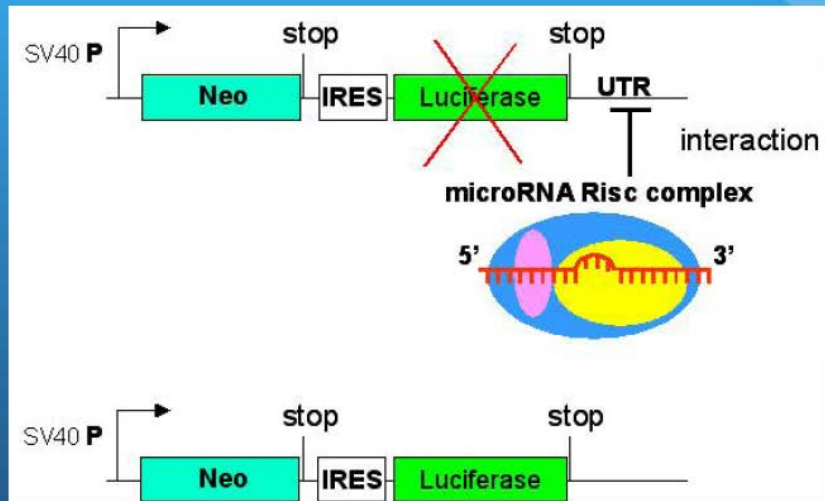
- Colonies from the ligation were screened using miniprep and digested to determine the correct clone.
- 5A and 9B was chosen due to their high concentrations of DNA.



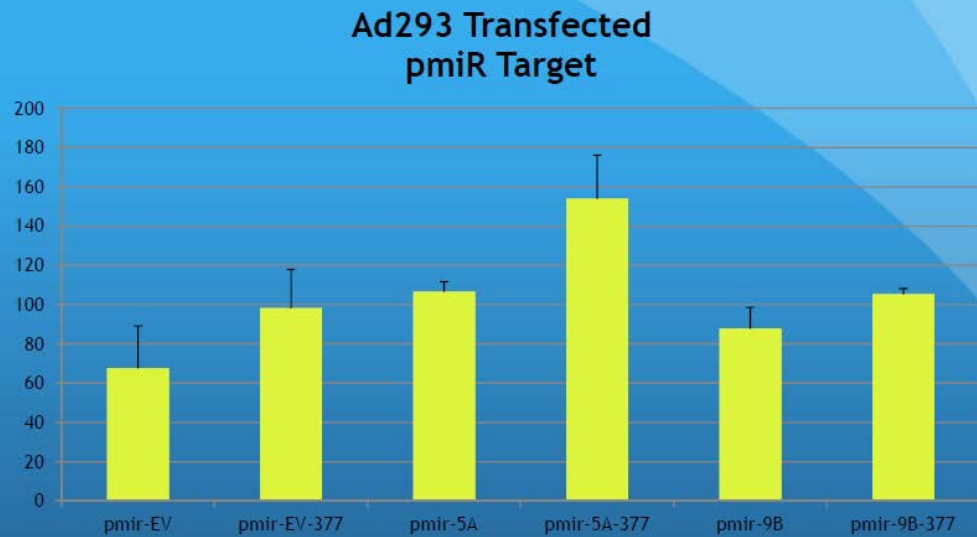


# Luciferase Assay

Reporter  
Clone



Control  
Clone



## Future Studies

- Clone Fragments 1 and 3 of the ETS-1 3' UTR as described earlier to determine whether miR-377 directly binds those regions.

# Conclusion

- miR-377 levels are lower in AA than EA men with PrCa
- miR-377 levels are lower in AA men with high grade versus low grade PrCa
- miR-377 does not directly target ETS-1 through the predicted site in fragment 2

## IMPACT

- Because miR-377 is lower in AA men with prostate cancer, this could be used as a non-invasive screening tool to better predict PrCa in AA men.

# Acknowledgments

- Dr. Victoria J. Findlay & Lourdes Nogueira
- Dr. Marvella Ford
- Hollings Cancer Center
- Dr. James B. Stukes



Improving Perceptions of Cancer  
Clinical Trials in South Carolina  
Ms. Laila Green

Abstract

Cancer is a major public health problem in the United States, where large racial differences in cancer mortality are evident. According to the American Cancer Society, for the majority of cancer types, African Americans (AA) have the highest cancer mortality rate and the lowest cancer survival rates of any other racial or ethnic group in the US.

*Underrepresentation of AA in Cancer Clinical Trials*

Unfortunately, although they have higher cancer mortality rates relative to their European American (EA) counterparts, AA are not well represented in cancer clinical trials. Clinical trials are needed to examine the impact of inequalities in income, education, barriers to high-quality health care, and racial discrimination on racial, ethnic, and ancestry differences in cancer mortality. These trials provide opportunities to test new screening techniques, therapies, and biomarkers that could reduce cancer disparities.

A major problem lies in the fact that despite bearing an unequal cancer burden, AA and Latinos continue to be underrepresented in clinical trials. While trial participation is of major importance for all people with cancer, it is of particular importance for AA. Proper sampling of a heterogeneous population to ensure sample representativeness is a key component of valid epidemiologic and clinical research. Without adequate numbers of AA in clinical trials, the generalizability of study results to members of this population is in question.

Insufficient representation of racially and ethnically diverse groups in clinical trials results in inequitable distribution of the risks and benefits of research participation and reduces generalizability of trial results. AA experience a disproportionate cancer mortality burden and therefore they should be included in cancer clinical trials in numbers that are commensurate with their burden of cancer, as the trials could identify ways to reduce the cancer burden in this population.

*Impact of Lack of Knowledge on Negative Perceptions of Cancer Clinical Trials and Recruitment*

The need to expand the knowledge base of cancer clinical trials among diverse community members is underscored by Ford et al. who reviewed sixty-five studies focusing on recruitment of racially and ethnically diverse participants to cancer clinical trials. Lack of education regarding cancer clinical trials was the most frequently reported barrier to participation. Similarly, Langford et al. report that lack of knowledge about clinical trials, and subsequent negative perceptions of them, are formidable barriers to the participation of diverse populations in trials.

Thus, lack of knowledge about trials can lead to negative perceptions of them, which in turn has a negative impact on trial participation. Unfortunately, negative perceptions of cancer clinical trials based on lack of knowledge can negatively impact trial recruitment in the very populations that could most benefit from the scientific knowledge gained through their participation. Fallowfield et al. argue that recruitment difficulties often arise from potential participants' lack of understanding of terms such as "randomization." Misperceptions in the randomization process (*i.e.*, for participants with cancer, the minimum level of care received is the best available current treatment rather than placebo) can also lead to suspicion on the part of potential participants about the ethical nature of the research.

# **Improving Perceptions of Cancer Clinical Trials in South Carolina**

**Laila Green**

**Summer Undergraduate Research Program 2012**



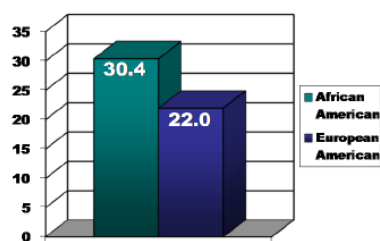
## **Presentation Outline**

- Identification of the Problem
- Conceptual Framework
- Role of Community Partners
- Implementation
- Dissemination
- Evaluation
- Sustainability and Future Goals

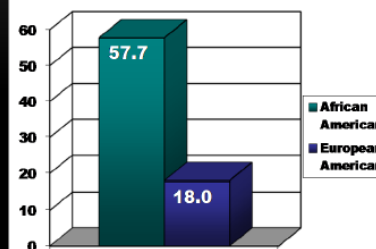
**Identification of the Problem:  
Cancer Is a Major Public Health  
Problem in South Carolina (SC)**

# Cancer Mortality For South Carolina Age Adjusted Rates: 2000 US Standard Population County: All Counties In South Carolina, 2008

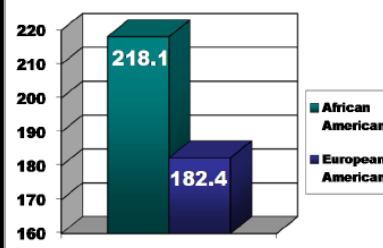
**Breast Cancer**



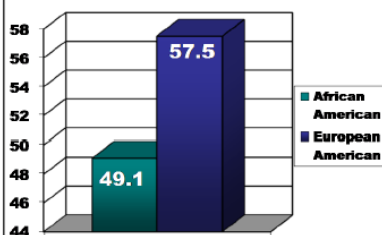
**Prostate Cancer**



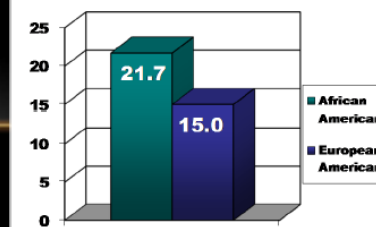
**All Cancers**



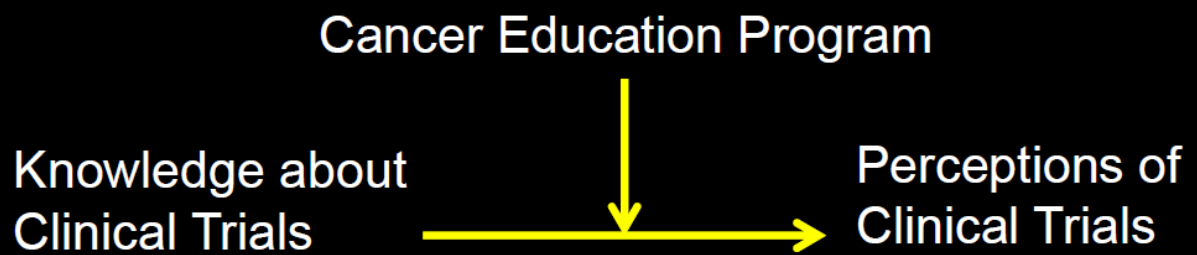
**Lung Cancer**



**Colorectal Cancer**



# Conceptual Framework

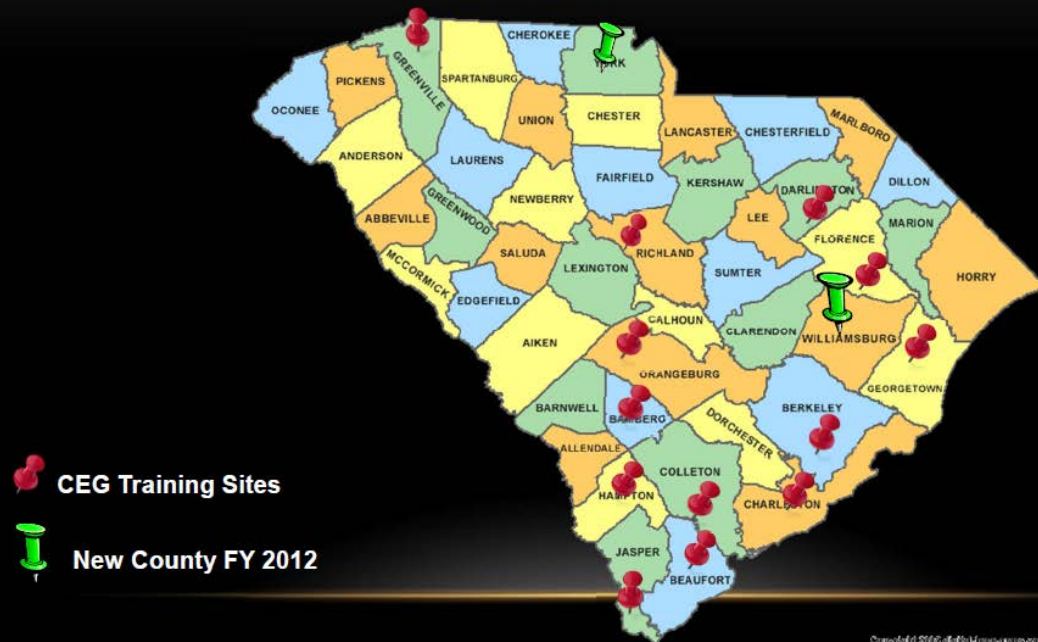


## **Description of the Statewide Cancer Education Program**

**4-Hour Cancer Education Program using a Train the Trainer design** funded by grants from AT&T and the Department of Defense (Grant Number W81XWH-10-2-0057, PI: Slaughter, MPI: Ford)

1. An evidence-based Cancer Education Guide developed by the South Carolina Cancer Alliance
  - 3-hour component focusing on general cancer knowledge
  - 30-minute component focusing on prostate cancer knowledge
2. A National Institutes of Health PowerPoint presentation that describes cancer clinical trials
  - 30-minute component focusing on cancer clinical trials information

# Statewide Cancer Education Program Service Area



# **Implementation And Dissemination**



## Role of Community Partners

- Community Partners
  - Identified program participants
  - Invited other local community organizations to jointly participate in the program
  - Selected venues for the program
  - Promoted the program in the local community
  - Recruited program participants
  - Assisted with the pre-registration process for the program

# Evaluation

## Measures

- **General sociodemographic information (e.g., age, race, income)**
- **General Cancer Knowledge**
  - 19-item instrument developed by the investigative team, (0-31 point scale)
- **Prostate Cancer Knowledge**
  - 10-item PROCASE instrument, (0-10 point scale) (Radosevich *et al.* 2004)
- **Perceived Self-Efficacy in Doctor-Patient Communication**
  - 5-Item PEPPI Scale, (0-5 point scale), (Maly *et al.* 2004; Maly *et al.* 1998)

Maly RC, Leake B, Silliman RA. Breast cancer treatment in older women: impact of the patient-physician interaction. *J Am Geriatr Soc* 2004;52:1138-1145.

Maly RC, Frank JC, Marshall GN, DiMatteo MR, Reuben DB. Perceived efficacy in patient-physician interactions (PEPPI): validation of an instrument in older persons. *J Am Geriatr Soc* 1998;46:889-994.

Radosevich DM, Partin MR, Nugent S, Nelson D, Flood AB, Holtzman J. *et al.* Measuring patient knowledge of the risks and benefits of prostate cancer screening. *Patient Educ Couns* 2004;143-152.

## Sample

- Residence in the communities near the location of the program site
- Male or female
- Any race or ethnicity
- Ages 21 years or older

# **Clinical Trial Perceptions Outcomes**

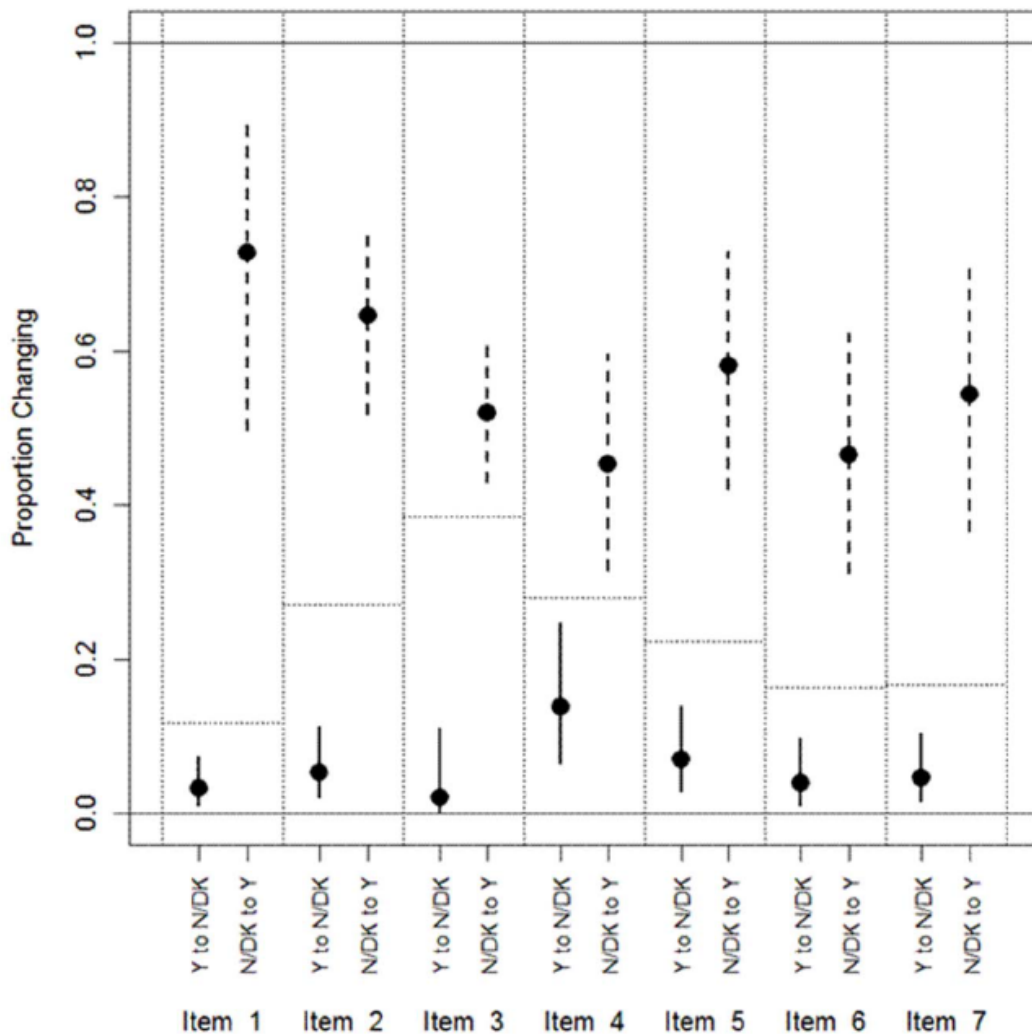
<b>Summary of Demographic Characteristics of Participants at Pre-test (N=195)</b>		
<b>VARIABLE</b>	<b>N</b>	<b>(%)</b>
<b>Age*</b>		
Less than 50 years	78	(41.1%)
51-64 years	73	(38.4%)
65-75 years	34	(17.9%)
More than 76 years	5	(2.6%)
<b>Hispanic*</b>		
Yes	3	(1.6%)
No	188	(98.4%)
<b>Race*</b>		
African American or Black	147	(77.4%)
American Indian or Alaskan Native	15	(7.9%)
Caucasian or White	28	(14.7%)
Other	0	(0.0%)
<b>Education*</b>		
Less than 8 years	4	(2.1%)
8-11 years	8	(4.2%)
12 years or completed high school	20	(10.5%)
Post high school training other than college	12	(6.3%)
Some college	41	(21.5%)
College graduate	53	(27.7%)
Postgraduate	53	(27.7%)
<b>Marital Status*</b>		
Married or living as married	88	(46.3%)
Widowed	19	(10.0%)
Divorced	24	(12.6%)
Separated	5	(2.6%)
Never married	54	(28.4%)
<b>Household Income*</b>		
\$0-\$19,999	47	(25.8%)
\$20,000-\$39,999	42	(23.1%)
\$40,000-\$59,999	41	(22.5%)
\$60,000-\$79,999	26	(14.3%)
\$80,000+	26	(14.3%)
<b>Gender*</b>		
Male	28	(21.2%)
Female	104	(78.8%)

Missing data on this variable

**Table 1. Fallowfield Instrument Items**

<p><b>1. Do you think that patients should be asked to take part in medical research?</b></p> <p>_____ Yes          _____ No          _____ Do not know</p>
<p>Suppose that you were asked to take part in a research study comparing two treatments, both of which were suitable for your illness.</p> <p><b>2. Would you be prepared to take part in a study comparing different treatments?</b></p> <p>_____ Yes          _____ No          _____ Do not know</p>
<p>Usually the only scientific way to compare one treatment with another is for the choice between the two to be made randomly, rather like tossing a coin.</p> <p><b>3. Would you be prepared to take part in a study where treatment was chosen at random?</b></p> <p>_____ Yes          _____ No          _____ Do not know</p>
<p>If you answered "No" or "Do not know" to Question 3, we would now like to ask you a bit more about this. In a randomized study a choice would be made between two treatments, either of which would be suitable for you. Your doctor and experts in the field do not know for sure if one treatment is better than the other, or if they are both the same, that's why they want to do the study.</p> <p><b>4. Would knowing that encourage you to take part?</b></p> <p>_____ Yes          _____ No          _____ Do not know</p>
<p>In a random choice study, if the treatment you were receiving did not suit you for any reason you could leave the study. Your doctor would then give you whatever other treatment might be appropriate for you.</p> <p><b>5. Would that encourage you to take part?</b></p> <p>_____ Yes          _____ No          _____ Do not know</p>
<p>Before you agreed to enter a random choice study the doctor would tell you all about the two treatments being compared, before you were allocated to one or the other.</p> <p><b>6. Would that encourage you to take part?</b></p> <p>_____ Yes          _____ No          _____ Do not know</p>
<p><b>7. If you knew all the following things were taken in account, would you change your mind and agree to take part in the study?</b></p> <ul style="list-style-type: none"> <li>▪ Both treatments were completely suitable</li> <li>▪ You could leave the study if the treatment did not suit you</li> <li>▪ There is plenty of information before the random choice was made</li> </ul> <p>_____ Yes          _____ No          _____ Do not know</p>





**Caption:** Proportion of respondents who changed from Yes to No/DK versus No/DK to Yes for the seven items in the Fallowfield instrument.  $P < 0.001$  for items 1, 2, 5, 6 and 7;  $p = 0.001$  for item 3;  $p = 0.008$  for item 4. Horizontal dotted lines show the assumed null proportion of respondents who change their response from baseline. Due to some missing responses, the sample sizes vary per item for items 1 through 7, respectively, as follows: 178, 177, 177, 118, 143, 146, 144.

## **Sustainability and Future Goals of the Cancer Education Training Program**

- The SC Cancer Alliance wrote a grant to cover the cost of two training sessions in 2012
- The SC Department of Health and Environmental Control will cover the cost of at least one training session in 2012
- The trained leaders are conducting sessions in their communities – we will evaluate whether their knowledge gains are sustained over time
  - 40 trained facilitators have conducted 104 sessions, reaching 3,292 individuals
- The model will serve as the foundation for a future R01 study with the HCC's statewide Cancer Clinical Trials Network

### **Biological Implications of DNA Glycation in Prostate Cancer**

**Introduction/Background:** Numerous studies corroborate the existence of biological factors that may influence racial disparities in cancer incidence and mortality rates. Prostate cancer is more aggressive among African-American men who also present poor survival rates compared to European American men. Studies show that this difference is not only associated with treatment availability or timing of prognosis, but that there are genetic and biological differences among ethnic groups that exist independently. A recent significant study was performed by the Southwest Oncology Group (SWOG) involving close to 20,000 cancer patients treated in randomized phase III clinical trials. The significance of this study weighs heavily upon previous studies because it controlled for prognostic, treatment and income factors prior to assessing between race and survival. The results of this study identify inherent genetic, biological and molecular characteristics in race-specific tumor samples as determinant factors for differences in breast, prostate and ovarian cancer disparities and not just discrepancies in treatment quality and/or social status.

One biological mechanism that may contribute to this difference is the presence and function of advanced glycated end products (AGEs). AGEs are the results of glycation which is a process that is engendered by glycolysis. Glycolysis is the process of metabolizing sugars to carbohydrates and exists within every human organism. The products of sugars can react non-enzymatically (glycate) with proteins, lipids and nucleic acids to promote the production of AGEs. AGEs are best

known for their role in diabetes, but have also been linked to aging, neurodegenerative disease and cancer. Increased sugar levels, extraneous glycolysis, oxidative stress and intracellular free radical activity are cancer associated processes that have been shown to elevate glycation activity leading to increased levels of AGE. Racial specific differences in AGE levels is hypothesized because there is a direct correlation between ingested and circulating AGE levels, oxidative stress and glycation induced DNA mutations which provide a mechanistic link between dietary carbohydrates and cancer[1]. AGE content in the Western Diet has consistently increased over the last 50 years. This provides a compelling rationale for examining glycation and AGE levels as a mechanism promoting racial disparity in prostate cancer. Though the function of AGEs as it contributes to diabetes is being further studied there is little consensus on the contributing functions of AGEs as it relates to cancer.

AGE binds to receptor-AGE (RAGE) which is a membrane bound receptor present on key cells involved in the immune and inflammatory response. RAGE is a key factor that contributes to creating and sustaining a pro-tumorigenic environment. Such activation results in the expression of inflammatory cytokines such as IL6, which are essential for communication between cancer cells and the surrounding stroma of the tumor. RAGE is over-expressed in a variety of tumor types including prostate. Clinical studies support a direct link between RAGE activation and proliferation, survival, migration, and invasion of tumor cells.

Earlier work from our laboratory using ELISA, demonstrate that the AGE metabolite carboxymethyl lysine is higher in serum from African American cancer patients than European American. (Highest CML levels were observed in the high grade African American tumors). This indicates that elevated AGE levels in African American prostate cancer patients may be a mechanism of cancer disparity.



# **“Biological Implications of DNA Glycation in Prostate Cancer Health Disparity”**

**Deidre White**  
**SURP student 2012**

## **Co-Principal Investigators:**

**Mahtabuddin Ahmed PhD**  
**Associate Professor**  
**South Carolina State University**

**David Turner PhD**  
**Assistant Professor**  
**Hollings Cancer Center**  
**Medical University of South Carolina**



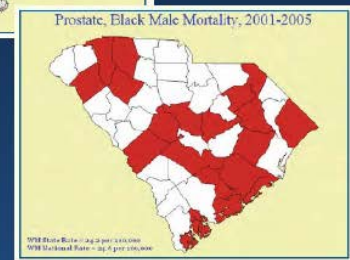
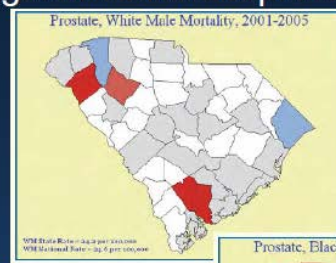
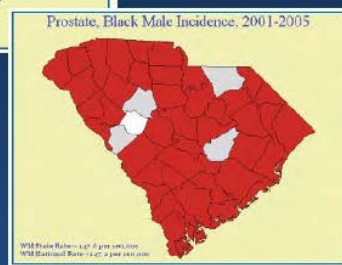
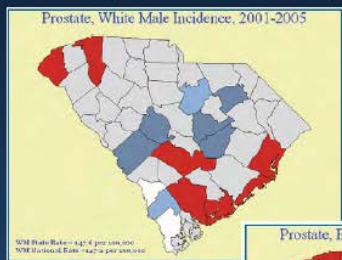
## Overview

- Prostate Cancer in South Carolina
  - Causes of Racial Disparities
- Glycation & AGEs
  - Exogenous AGEs
  - receptor-AGE (RAGE)
  - AGE & Cancer
- Hypothesis
- Results
  - AGE
  - RAGE
  - NF- $\kappa$ B
- Conclusions, Discussion
- Acknowledgments



# Prostate Cancer in South Carolina

- SC has one of the highest densities of AA population in the US
- Rates of new cases of prostate cancer among Black men in SC are about 80% higher than in White men, vs. 55% nationally
- Death rates in SC-AA men are almost 3 times that observed in SC-EA men
- Racial difference in death rates and aggressiveness of prostate cancer are especially striking at younger age



Source: [sccanceralliance.org](http://sccanceralliance.org)



## Causes of Cancer Health Disparities

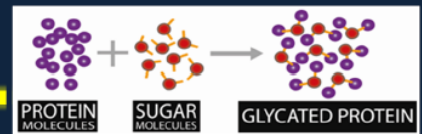
- **Socioeconomic factors**
  - Income, diet, education level, living conditions
- **Standard of care**
  - Lack of health coverage, isolated communities, physical/cultural beliefs
- **Behavioral risk factors**
  - smoking, lack of exercise, obesity, excessive alcohol
- **Environmental factors**
  - work/living environment, passive smoking, emigration, chemical exposure

**It is now clear that cancer health disparity also exists due to molecular differences in tumor biology**

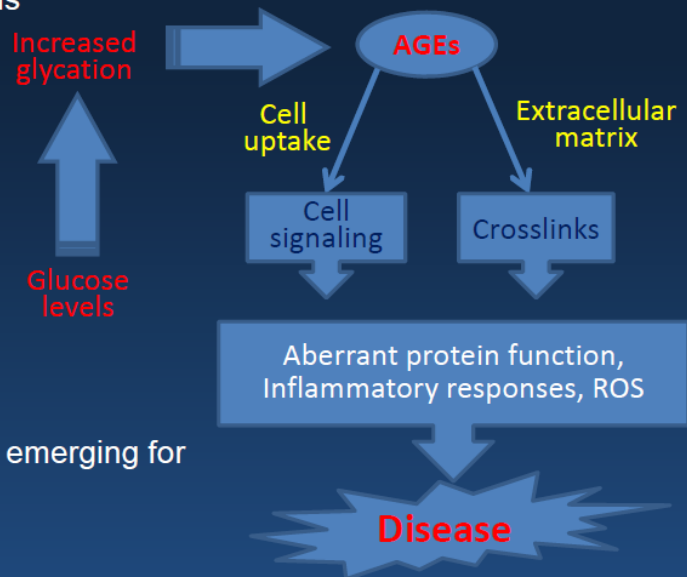
- Cancer health disparity still exists after controlling for socioeconomic and standard of care issues (SWOG)
- Sparse information exists about the genetic and biological factors that contribute to cancer health disparity



# Glycation & AGEs



- Is the non-enzymatic reaction of glucose with proteins, phospholipids and DNA
- Glycation produces reactive metabolic adducts known as Advanced Glycation End products (AGEs)
- AGEs result in protein denaturation and can function as receptor ligands
- Pathological effects of elevated AGEs include increased inflammation, ROS and stress responses
- Elevated AGEs are associated with Alzheimer's disease, type II diabetes, stroke, high blood pressure, kidney disorders, and autoimmune diseases
- A role in cancer progression is now emerging for reactive metabolites



## Exogenous AGEs

- Exogenous AGEs are also accumulated in the body through the ingestion of food
- AGE content in western diets has steadily increased over the last 50 years



High fat foods



Processed foods



Sodas



Heavily cooked foods



Artificial coloring



High sugar foods



## AGE receptor (RAGE)



### Structure

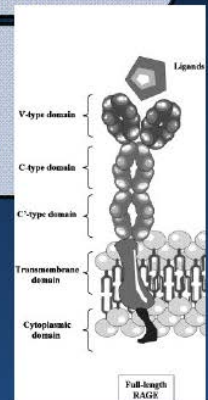
- RAGE is the best characterized receptor for AGEs
- Composed of an extracellular domain, three immunoglobulin domains, a single transmembrane domain and a cytoplasmic tail
- full-length RAGE consists of 404 amino acids and is 48-55 kDa in size

### Function

- RAGE is also activated by HMGB1 and S100 family members
- RAGE activates different cellular signaling pathways depending on the individual cell type
- Like AGEs RAGE promotes inflammation, ROS and stress responses

### Cancer

- RAGE is overexpressed in a variety of tumor types
- Links between RAGE activation and cell survival, migration, invasion and inflammation has been demonstrated in cancer
- Blockade of the RAGE signaling axis suppresses tumor growth in mouse models



# AGEs and cancer

## Warburg Effect

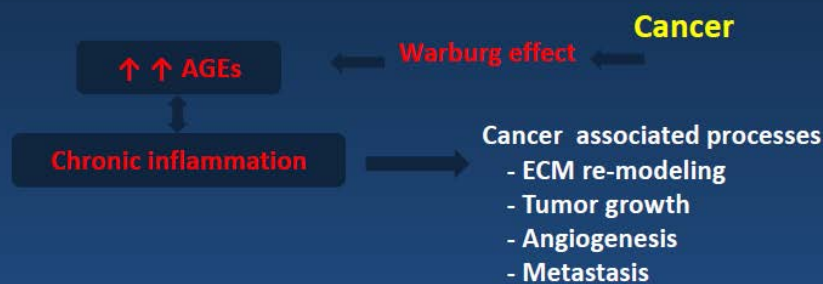
- Normal cells rely on mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes
- Cancer cells instead rely on aerobic glycolysis to generate ATP by increasing glucose levels (Warburg Effect - 1924)

## Glycation

- Tumors are therefore characterized by high glucose levels which fuels the Warburg effect
- High glucose levels in the cell results in higher levels of glycation and AGEs

## AGEs

- AGE levels are elevated in several tumor types
- They promote cancer associated processes - migration and invasion
- AGEs act as ligands for receptors and alter cell signaling pathways (e.g., RAS, NFkB, JAK/STAT.)





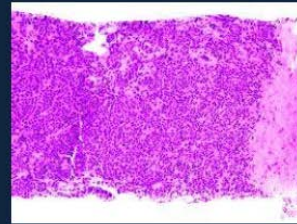


## Study hypothesis

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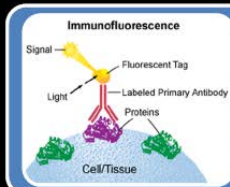
**Elevated AGE metabolites may influence risk of cancer and/or cancer prognosis and define a metabolic susceptibility difference driving cancer health disparity**

## Tissue and serum samples:



16 low grade prostate cancer

## Tumor AGE levels



### Tumor AGE levels – Fluorescent AGE staining

- Slices of normal and cancerous prostate tissue are mounted on slides, prepared and probed with anti-AGE antibodies
- A second fluorescent antibody is bound to the first AGE antibody and visualized under a fluorescent microscope

Control



## AGE expression in cell lines

Serum free media

DU145

PC3

Serum control



AGE Ab

### Western blot

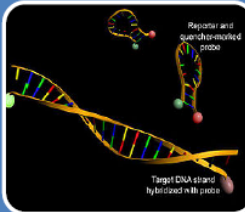
- This has led us to hypothesize that two types of AGE metabolite exist in cancer
  - Long term – accumulated in the body as we get older
  - Short term – secreted by the cancer cells themselves





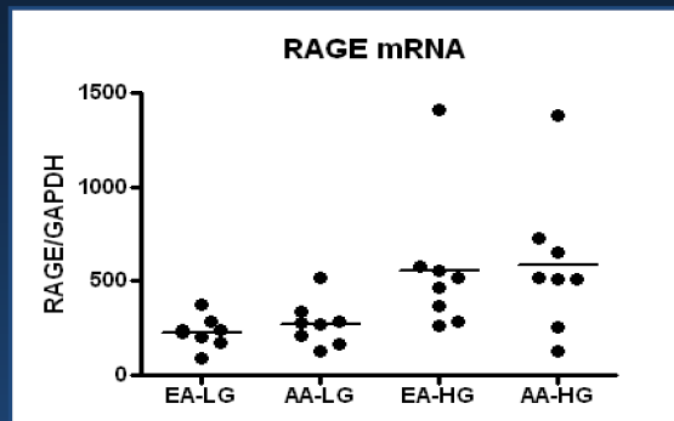


# RAGE expression in Pca tumors



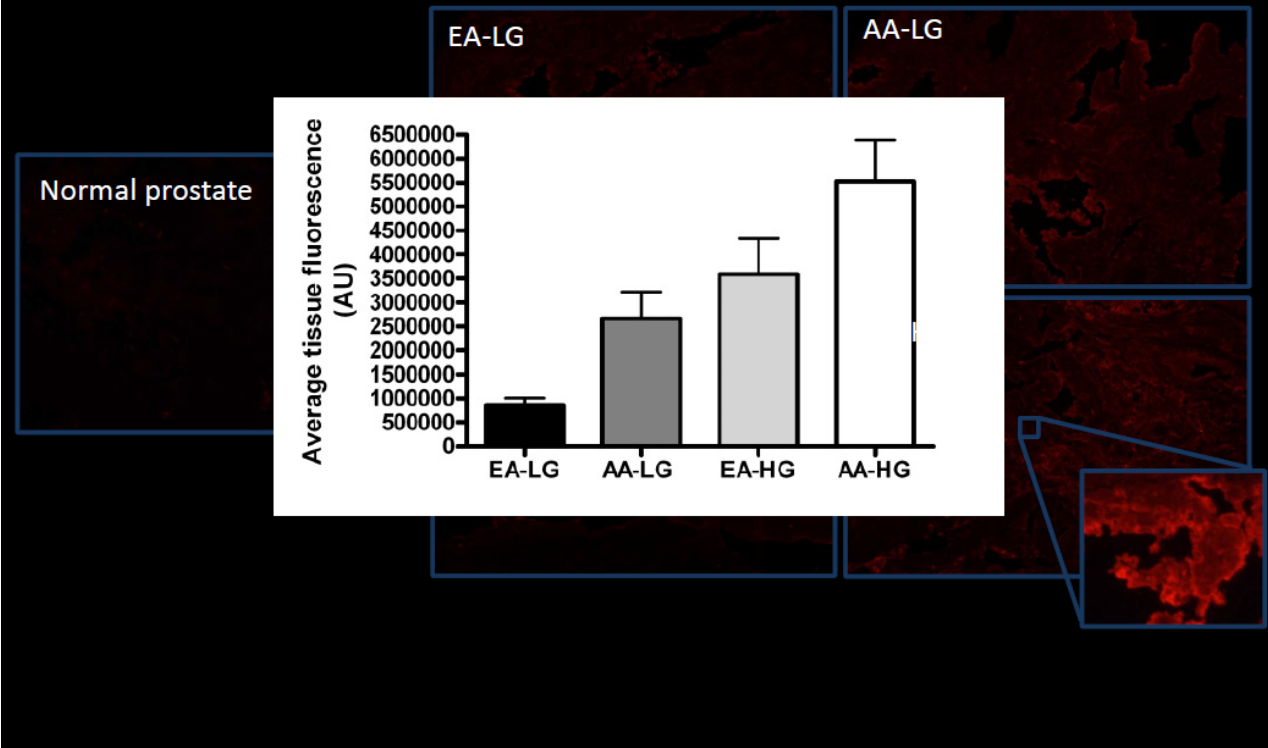
## mRNA expression – Probe based real time PCR

- Probe reporter fluorescence is quenched due to FRET.
- Probes and the complementary DNA strand are hybridized and reporter fluorescence is still quenched.
- During PCR, the 5'-ends of the probe are degraded by the Taq polymerase and the fluorescent reporter is released.

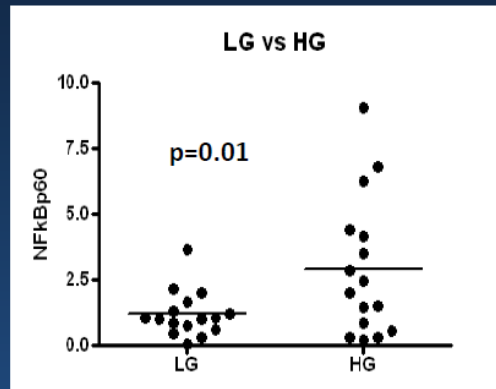
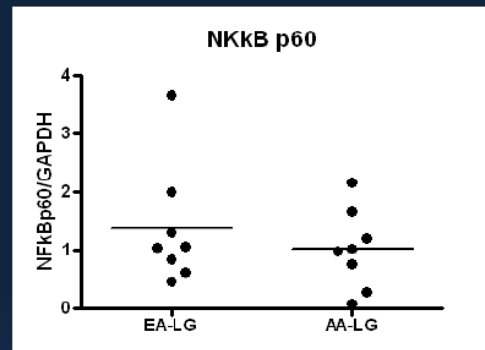
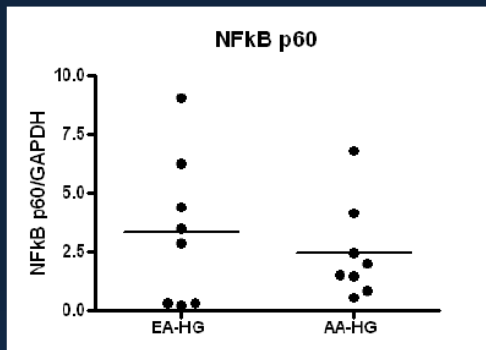


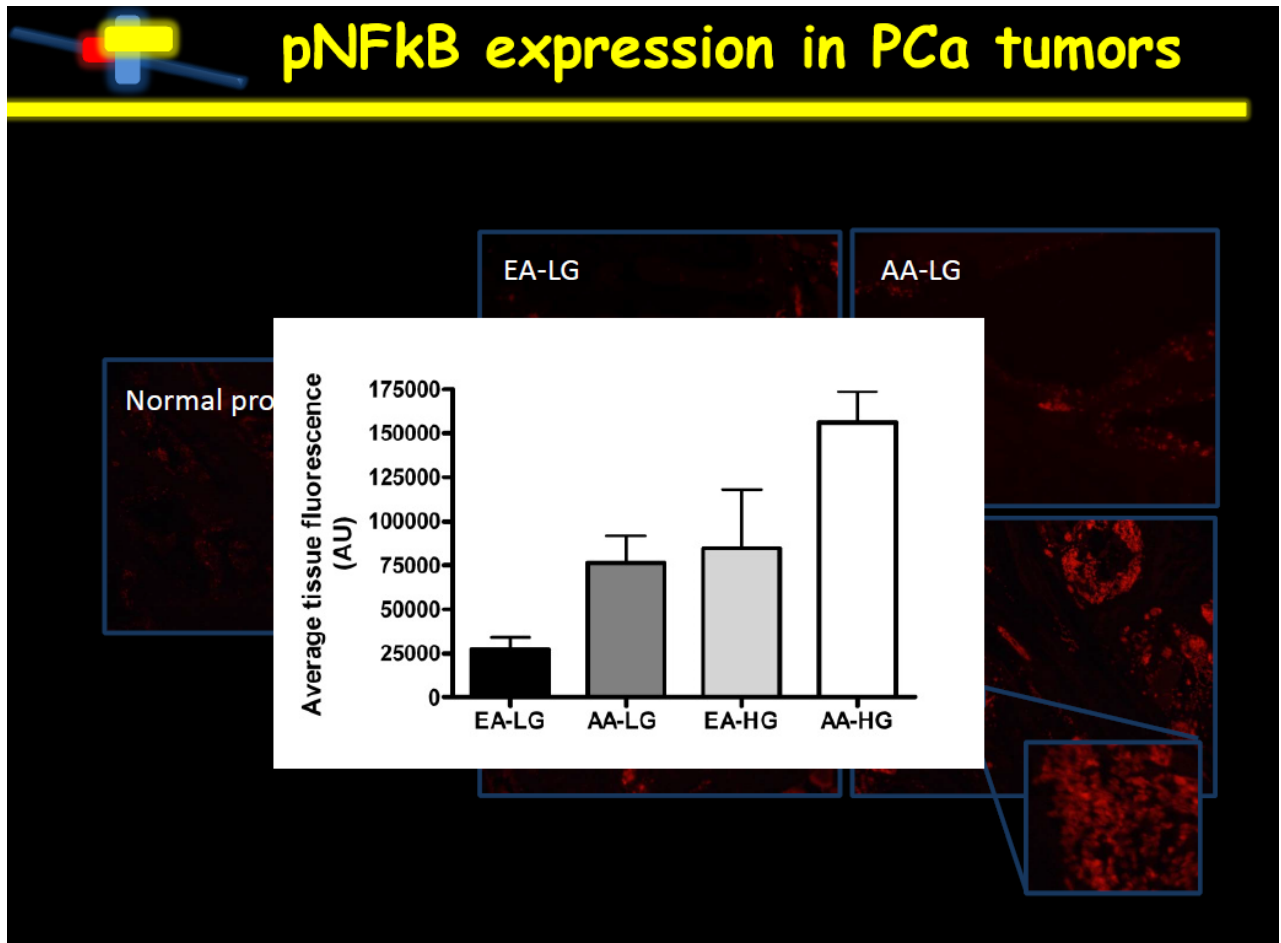


## RAGE expression in PCa tumors



## NFkB expression in PCa tumors





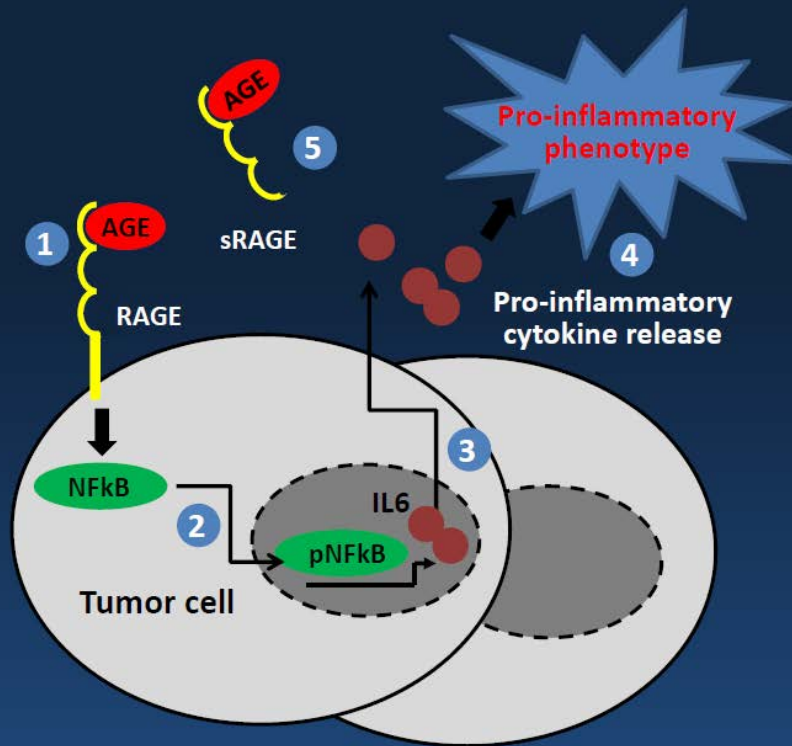


## Impact on health disparity

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- A greater understanding of the risk factors and biological links associated with cancer = significantly impact African American communities
- Elevated AGE metabolites may influence risk of cancer or cancer prognosis and define a metabolic susceptibility difference driving cancer health disparity
- By assessing overall AGE and pro-inflammatory cytokine profiles we may define prognostic/diagnostic markers to guide treatment strategies for aggressive disease
- Given the potential role of dietary-AGE in promoting cancer, opportunities also exist for cancer prevention initiatives arising through health nutritional education

## Our Model



# Acknowledgements



**Dion Foster**  
MS student



**Dr. Judith Salley,**  
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SC



**Dr. Marvella Ford,**  
Associate  
Professor,  
Department of  
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SC



**Dr. David Turner,** Assistant Professor  
Department of Pathology and  
Laboratory Medicine, MUSC, SC



**Funding –**  
NIH/NCI P20 Award  
HCC disparities research  
pilot project



## **Appendix D: Academic Accomplishments to Date of the 2012 Student Fellows**

**Year of Program Participation: 2012**

❖ These are current student fellows participating in the 2012 SURP program. Therefore it is too early to report additional accomplishments at this time. Many accomplishments are expected to occur during the course of the next few years following their participation.

Student Name	Summer Research Project	Funding Source	Publications, Presentations and Honors	GRE Status	Graduate School Admission
Ms. Sylvia Bridges Junior SC State University	<b>Mentor:</b> Dr. Victoria Findlay <b>Research Project:</b> The Effects of MiRNA on Prostate Cancer	Department of Defense (SE VIEW)	<b>Publication:</b> No publications to date <b>Presentation:</b> 2012 MUSC Summer Undergraduate Research Program	Has taken the GRE.	Currently enrolled in a Doctor of Chiropractic Program at Life University in Marietta, GA.
Ms. Deidra White First-Year Student SC State University	<b>Mentor:</b> Dr. Dave Turner <b>Research Project:</b> Implications of DNA Glycation Affecting Correlation of Racial Disparities in Prostate Cancer	National Institutes of Health/ National Cancer Institute	<b>Publication:</b> No publications to date <b>Presentation:</b> 2012 MUSC Summer Undergraduate Research Program	Has not taken the GRE.	Still an undergraduate at SC State University.
Ms. Myshayla Bell Sophomore Claflin University	<b>Mentor:</b> Dr. Shikhar Mehrotra <b>Research Project:</b> Overexpression of an Antigen in Melanoma Tumors and the Surrounding T Regulatory Cells using Immunohistochemistry	Department of Defense (HBCU)	<b>Publication:</b> No publications to date <b>Presentation:</b> 2012 MUSC Summer Undergraduate Research Program  Has an oral presentation scheduled	Has not taken the GRE.	Still an undergraduate at Claflin University.
Ms. Jasmine Fox Sophomore SC State University	<b>Mentor:</b> Dr. Erika T. Brown <b>Research Project:</b> The Role of RAD51 in Triple Negative Breast Tumor Progression/Relationship Between Breast Cancer and Metabolic Syndrome	Department of Defense (HBCU)	<b>Publication:</b> No publications to date Research Program <b>Presentation:</b> 2012 MUSC Summer Undergraduate 2012 Perry Halushka Student Research Day	Planning to take the GRE in March 2014.	Still an undergraduate at SC State University.
Ms. Claudia Thompson (Participated in the Training Program in the Summer of 2011 and the Summer of 2012)  Senior SC State University	<b>Mentor:</b> Dr. Danyelle Townsend <b>Research Project:</b> The Effects of PDI Inhibitors on S-Glutathionylation in Prostate Cancer Cells	Department of Defense (HBCU)	<b>Publication:</b> No publications to date <b>Presentation:</b> 2012 MUSC Summer Undergraduate Research Program	Has not taken the GRE.	Enrolled in a Master of Science Degree in Transportation (MST) at SC State University.

### Year of Program Participation: 2012

❖ These are current student fellows participating in the 2012 SURP program. Therefore it is too early to report additional accomplishments at this time. Many accomplishments are expected to occur during the course of the next few years following their participation.

Student Name	Summer Research Project	Funding Source	Publications, Presentations and Honors	GRE Status	Graduate School Admission
Ms. Laila Green Sophomore Claflin University	<b>Mentor:</b> Dr. Marvella E. Ford  <b>Research Project:</b> Improving Perceptions of Cancer Clinical Trials in South Carolina	Department of Defense (SE VIEW)	<b>Publication:</b> No publications to date  <b>Presentation:</b> 2012 MUSC Summer Undergraduate Research Program	Has not taken the GRE.  Too early to take the GRE	Still an undergraduate at Claflin University.
Ms. Britney White Senior Claflin University	<b>Mentor:</b> Dr. Patrick Woster  <b>Research Project:</b> Cancer Epigenetics: Using MTS Assays to determine cytotoxicity in drugs containing LSD1 and DNA methylation inhibitors	Department of Defense (HBCU)	<b>Publication:</b> No publications to date  <b>Presentation:</b> 2012 MUSC Summer Undergraduate Research Program  Two presentations: 2013 July Oral Presentation at Claflin University Summer Symposium  2014 Feb. Oral Presentation at ERN Emerging Researchers National Conference in STEM Washington DC. Won second place for her oral presentation.	Has not taken the GRE  Scheduled to take the GRE in March 2014	Applying to graduate school.